ANNALS OF
INTERNAL MEDICINE

ACUTE SUPPURATIVE BRONCHITIS AND BRONCHIOLITIS IN CHRONIC PULMONARY DISEASE: DIAGNOSIS AND MANAGEMENT *

By LEONARD CARDON, M.D., F.A.C.P., *Chicago, Illinois,* LOUIS
LEMBERG, M.D., *Miami Beach, Florida,* and REGINA S.
GREENEBAUM, M.D., *Kerrville, Texas*

AN episode of acute bronchitis ingrafted on chronic asthmatic bronchitis, emphysema, pulmonary fibrosis or bronchiectasis may so obstruct the bronchi as to precipitate an acute respiratory emergency and cause death by suffocation.   A better understanding of the pathogenesis and pathologic physiology of this condition has made possible its earlier recognition and more effective treatment.   The most valuable therapeutic measures are: repeated aspiration of the tracheo-bronchial tree, administration of oxygen in the highest possible concentration, and the use of bronchodilator, vasoconstrictor, chemotherapeutic and antibiotic agents by aerosol inhalation, orally and parenterally.

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY

The chronic pulmonary diseases whose presence is essential for the development of this syndrome include, singly or in various combinations, emphysema, bronchial asthma, bronchitis, fusiform and saccular bronchiectasis, and fibrosis secondary to exposure to irritating dusts or to pulmonary infections or malignancies.

Chronic pulmonary emphysema is present in all of these patients.   The lungs are inelastic, distended and voluminous.   The essential pathologic change [1] is a primary degenerative atrophy of the alveolar wall of unknown origin which leads to thinning and breaking down of the alveolar septa, coalescence of alveoli into larger alveolar sacs, distention of persisting alveoli, narrowing and destruction of alveolar capillaries, and loss of pulmonary elasticity.   Localized narrowing and tortuosity of the bronchioles and

alveolar ducts are always present. The loss of pulmonary elasticity leads to disturbances in the mechanism of breathing. The hyperdistended lungs depress and flatten the diaphragm, and raise the ribs more or less to an inspiratory position, thus diminishing their inspiratory excursion. Expiration is transformed from the normal passive recoil of the distended elastic lung to a voluntary act of contraction by the respiratory muscles. The intrapleural pressure at the end of expiration approaches that of the atmosphere and hinders the expiratory ascent of the diaphragm. These three factors together—the diminution of the pulmonary capillary bed, which leaves many alveoli relatively avascular; the partial occlusion of the bronchioles and alveolar ducts, which permits blood to flow through relatively unaerated portions of the lungs and remain unoxygenated, and the mechanical disturbances in respiration—all contribute to anoxemia in this disease. The anoxemia leads to compensatory hyperventilation, in severe cases even at rest, and the resulting inefficient, rapid, shallow breathing further diminishes the oxygen saturation of the arterial blood. In certain portions of the lungs where bronchi and alveolar ducts are partially occluded, hyperventilation increases the negative pressure during inspiration. This has the effect of sucking serum from the alveolar capillaries, thus creating areas of focal pulmonary edema. Mucus is similarly sucked from the mucous glands of the bronchi into their lumens, with consequent increase in dyspnea, cough and expectoration. In severe cases the vital capacity is markedly diminished and may approach or equal the tidal air. The residual ("dead") air is markedly increased. The tidal air, or effective respiratory air flow per breath, may be only slightly changed but the lungs have little or no power to compensate for any considerable degree of bronchial obstruction by increased depth of respiration; rather, respiration becomes rapid and shallow.

Bronchial asthma is present in many of these patients. Its pathologic physiology is related to intermittent attacks of spasm of the bronchial circular smooth musculature.[1,2] Edema of the mucosal lining and excessive bronchial secretion of a peculiarly viscid type, with formation of inspissated mucous plugs, contribute to the bronchial narrowing and occlusion and the production of the characteristic symptoms, dyspnea and wheezing. A functional type of emphysema, usually acute and transient, develops during attacks. In the normal persons, the bronchi dilate during inspiration and contract during expiration. In bronchi already pathologically narrowed, the further narrowing during expiration results in a valvelike action whereby a greater volume of air enters the alveoli during inspiration than can escape through the narrowed bronchial lumen during expiration. More and more air remains trapped in the alveoli with each respiration, and this leads to progressive alveolar distention and functional emphysema. The obstruction of certain bronchioles and alveolar ducts produces increased negative pressure during inspiration in the parts of the lungs to which they lead. As in emphysema, this increased negative pressure exerts a suction effect on serum from the alveolar capillaries and mucus from the bronchial mucous

glands, producing areas of focal pulmonary edema and increased bronchial secretion, dyspnea, cough and expectoration. The initial sensation of dyspnea at the onset of an attack of asthma is due to the mechanical difficulty of drawing air through the narrowed bronchi. As the attack lasts, and the factors of insufficient pulmonary ventilation due to the narrowed bronchi, progressive functional emphysema and increased pulmonary and bronchial secretion interfere with oxygen diffusion into the alveolar capillaries, arterial anoxemia contributes to the dyspnea.

Chronic bronchitis is frequently present. The pathologic changes are variable. In some cases, congestion, edema and thickening of the bronchial mucosa are found. In others, atrophy of the mucosa is predominant. Areas of desquamation of the lining epithelium, including the ciliated cells in the large bronchi, or actual ulceration occur, together with fibrosis and thickening of the submucosa, hypertrophy and contraction of the bronchiolar smooth muscle, cellular infiltration of the bronchial wall and mucous or mucopurulent secretion in the bronchial and bronchiolar lumen. Partial or complete obstruction of the bronchi by the viscid secretion may lead to localized areas of emphysema or atelectasis. Chronic cough and mucopurulent expectoration characterize this condition clinically. In the elderly the disease is often associated with wheezing and is then commonly called "asthmatic bronchitis." This term is evidence of difficulty in determining whether infectious bronchitis is the primary pathologic change which, reflexly by irritation, or secondarily by the development of bacterial allergy, produces bronchial spasm and asthmatic wheezing, or whether true allergic asthma is first present and is complicated by a superimposed infectious bronchitis.

Pulmonary fibrosis is often present and is usually secondary to chronic occupational exposure to irritating dusts or to some chronic pulmonary infectious or neoplastic process. Thickening of the alveolar membrane interferes with gaseous exchange and leads to an intractable type of anoxemia and carbon dioxide retention. Contraction of the lung and loss of its elasticity diminish pulmonary volume and vital capacity. Distortion of the bronchi with the production of localized strictures, torsions and dilatations occurs. Constriction and obliteration of alveolar capillaries contribute to the anoxemia and may lead to pulmonary hypertension and secondary chronic cor pulmonale. Fibrous pleuritis and mediastinal displacement, with resulting torsion of the great vessels at the base of the heart, are frequently associated conditions.

Bronchiectasis, fusiform or saccular, is a common concomitant of other chronic pulmonary diseases in this group. The dilated, chronically inflamed bronchi produce much mucopurulent secretion, which leads to chronic coughing and profuse, often fetid expectoration, usually worse on arising. Temporary complete obstruction of a bronchus draining a bronchiectatic cavity may lead to retention of infected secretions and spread of infection to produce a peribronchial pneumonitis.

In the presence of these chronic pulmonary disabilities, either singly or in

combination, the lungs are in a state of precarious "pulmonary compensation" which depends for its continuation on the maintenance of sufficient patency of the bronchial lumen, restricted though it may already be, to permit adequate respiratory gaseous exchange and expectoration of secretions. A potent cough reflex is essential to clear the air passages of secretions.

In these circumstances, the superimposition of acute diffuse bronchitis and bronchiolitis results in further encroachment on the restricted bronchial lumen and may lead to rapid and critical "pulmonary decompensation" with asphyxial death. This is in contrast to the situation in adults with previously normal lungs and bronchi. The diameter of their bronchial passageways is so large that even severe bronchitis rarely produces enough narrowing to cause serious asphyxia or endanger life.

The development of this illness is marked by acute hyperemia and edema of the bronchial mucous membrane, which becomes congested and swollen and very early is covered with a tenacious, viscid and stringy mucus. As the disease progresses, if the patient lives long enough, the bronchial exudate gradually becomes more mucopurulent and abundant and tends to fill the bronchi and bronchioles. In those patients with asthmatic propensity, intermittent or continuous spasm of the bronchial smooth muscle further acts to narrow the bronchial lumen. In the presence of this increased bronchial narrowing and obstruction, and the hyperventilation induced by the rapidly progressive anoxemia, the markedly augmented negative pressure during inspiration, as explained previously, produces focal pulmonary edema and increased bronchial exudate. The acute narrowing of the bronchi, caused by the rapidly progressive swelling of the mucous membrane, spasm of the bronchial muscle and accumulation of secretion, leads to increasing anoxemia which ultimately becomes so severe that the cerebral and medullary vital centers are depressed to the point of complete loss of the cough reflex. The bronchioles and bronchi then become completely filled by secretion and death occurs by "drowning" and suffocation.

CLINICAL PICTURE

The clinical picture is quite characteristic. The patient is usually past middle age or elderly, more frequently male than female, and has been in more or less chronic ill health for many years, with constant or periodic cough, expectoration, dyspnea on exertion or even at rest, or asthmatic wheezing. A history of previous or present occupational exposure to a dusty environment is often obtained. An underlying predisposing systemic disease, such as uncontrolled diabetes mellitus, may be present. At the onset of an acute upper respiratory infection, grippal symptoms, rhinitis, pharyngitis or laryngitis may be very mild and may cause the patient no great concern. As the infection travels downward in the respiratory tract, acute tracheitis and bronchitis develop. Dull presternal pain and soreness aggravated by breathing and coughing may appear. Cough, dyspnea and

wheezing increase and may be accompanied by mild fever and tachycardia. Early, during the stage of congestion of the bronchial mucosa, before any appreciable secretory response to the acute inflammatory process appears, little if any expectoration will occur, or the amount of expectoration previously present, as in patients with bronchiectasis, may be sharply reduced because of the narrowing of the bronchi. During this stage the cough is dry and harsh. Gradually secretion of mucus increases. The expectorated sputum is at first gray-white, viscid and stringy, and is brought up with difficulty. Gradually it becomes more abundant and mucopurulent and the cough "loosens up." Thus far the clinical picture is common enough, and in the majority of cases the acute infection subsides uneventfully, leaving the patient in his usual state of chronic ill health.

In the minority of cases here described, the acute bronchial inflammation does not subside but becomes progressively worse and leads to increasing narrowing of the bronchi and their occlusion by accumulating secretion. This results in increasing dyspnea, cough and tachycardia. Cyanosis appears or, if previously present as part of the chronic pulmonary illness, becomes more intense. The patient is now critically ill. As anoxemia increases, anxiety, restlessness and apprehension become part of the picture and periods of disorientation and delirium occur. Air hunger causes violent activity. The patient tosses about or periodically sits up in great excitement, forcefully gasping for air. The canopy of the oxygen tent is frequently cast aside or torn as he struggles in his efforts to breathe. The tachypnea, restlessness, constant coughing and inability to take nourishment because of the constant fighting for air lead to early exhaustion of the patient and weakening of the cough so that it becomes more and more ineffectual in clearing accumulating secretion.

Physical examination at this stage reveals a critically ill patient. Inspiratory contraction of the accessory muscles of respiration in the neck may be marked. The chest is usually emphysematous, with increased anteroposterior diameter. The lungs are hyperresonant throughout, especially at the bases posteriorly. Diffuse sibilant and sonorous breath sounds or, in the late stages, harsh rhonchi, and medium and coarse or bubbling moist râles are heard throughout both lungs. These are more marked in the bases posteriorly in cases with previous chronic bronchitis or bronchiectasis. In uncomplicated cases, fine râles are not present. Inspiratory retraction of the supraclavicular and infraclavicular spaces, the suprasternal notch and the inferior costal arches anteriorly may be present, but this often is not marked because of the barrel chest and the fixation of the ribs in the inspiratory position. Stridor is not a feature because of the diffuse nature of the obstruction in the distal smaller bronchi and alveolar ducts rather than in the larynx, trachea or main bronchi.

In the final stage, stupor and then coma set in, with asphyxial depression of the brain and the vital centers in the medulla, clinically evidenced by loss

of the deep and superficial reflexes, absent corneal reflex, widely dilated, fixed pupils; fibrillary muscle twitchings; shallow, irregular, gasping respirations; rapid, weak irregular pulse; very low blood pressure, which may drop to shock levels, and complete loss of the cough reflex. This stage may last for as long as three days. The complete loss of the cough reflex results in absolute inability of the lungs to clear themselves of accumulating secretion, and death ensues from "drowning" and suffocation. The toxicity of the infection is usually not a factor in causing death. Fever is usually low grade or absent but moderate leukocytosis may occur. The course of the illness can be extremely rapid, and its progress from the onset of acute pulmonary symptoms to asphyxial death may occur in from 12 hours to three days.

DIAGNOSIS

The diagnosis is facilitated by familiarity with this syndrome and knowledge that it can be precipitated in an individual with chronic pulmonary disease by an acute upper respiratory infection. The most important single point in the diagnosis is the history of a recent "cold." It is essential that this history, if not voluntarily offered, be sought by direct questioning, since the "cold" is often so mild and its progress to the bronchial system so insidious that it is forgotten by the patient and his family, and the onset of the illness is dated from the beginning of the more spectacular critical pulmonary symptoms. These symptoms are interpreted as representing an exacerbation of the patient's asthma or bronchitis, and their connection with the grippal symptoms, rhinorrhea, sneezing, sore throat or hoarseness of several days before is not appreciated by the patient or his relatives. The importance of the history of a recent "cold" cannot be stressed too strongly. If sought, it is almost invariably found, and once the patient recalls its occurrence he also frequently recognizes the fact that the "cold" never really disappeared but progressed into his present illness.

The two most common incorrect diagnoses are acute left ventricular failure (with or without acute myocardial infarction), and pneumonia.

That acute pulmonary edema secondary to acute left ventricular failure is frequently diagnosed is understandable when one considers that the patient is usually past middle age and may have evidence of coincidental generalized arteriosclerosis or hypertension. The onset of illness is often hyperacute, and the patient is at once precipitated into a critical state. The severe dyspnea, orthopnea, cyanosis, cough, wheezing, and sibilant, sonorous and moist pulmonary râles are interpreted as cardiac asthma. Where no other cause is apparent, the diagnosis of "silent" myocardial infarction may be considered as the basis of the presumed acute left ventricular failure. Careful consideration will usually eliminate the diagnosis of heart failure. In uncomplicated cases of this syndrome, cardiac abnormalities are characteristically absent. The heart is small and the rate regular, though rapid. No murmurs, jugular engorgement, hepatic enlargement or peripheral edema

are found.   Pulmonary râles are usually scattered and are not predominantly basal unless chronic bronchitis or bronchiectasis has been present previously.   Roentgen-ray examination discloses the hyperaeration, wide interspaces and depressed diaphragm of emphysema, the accentuated markings and ground glass appearance of fibrosis, or evidence of chronic bronchitis or bronchiectasis.   The characteristic hilar and basal vascular engorgement of chronic pulmonary passive congestion and the cardiac dilatation of heart failure are not seen.   Absence of chest pain and of characteristic abnormalities in serial electrocardiograms eliminates the diagnosis of myocardial infarction.   The patient with chronic pulmonary disease who develops acute bronchitis and bronchiolitis may also coincidentally have degenerative heart disease with cardiac enlargement, valvular murmurs, auricular fibrillation and electrocardiographic evidence of chronic coronary artery abnormalities. Under such circumstances, the differential diagnosis between acute bronchiolitis and acute left ventricular failure may be very difficult, and may depend for its solution on the rapid response of the latter to appropriate cardiac treatment.   In most cases, rather than risk the consequences of a mistake in diagnosis, both conditions should be treated simultaneously.   Acute bronchial infection may occur in a patient who already has or rapidly develops right heart failure manifested by jugular engorgement, hepatic enlargement and peripheral edema.   The symptoms of right heart failure are not pulmonary and present no problem in the differential diagnosis of acute bronchiolitis.   As a rule, right heart failure as a result of cor pulmonale is not a factor in the cases described.

Bronchopneumonia is as often mistakenly diagnosed in this disease as heart failure.   Acute dyspnea, cyanosis, cough, expectoration, fever, leukocytosis and scattered moist râles are frequently interpreted and diagnosed as bronchopneumonia of the "atypical" or "virus" type, and the critical state of the patient is entirely attributed to this.   Hemoptysis, common in pneumonia, is absent in uncomplicated bronchiolitis.   As a matter of fact, the moist râles present in this syndrome are medium or large and never the crepitant râles of pneumonia.   Furthermore, most of them disappear when the trachea and bronchi are thoroughly aspirated by mechanical suction through a catheter or bronchoscope.   This disappearance proves that they arise in the bronchi and therefore cannot be of pneumonic origin.   While foci of bronchopneumonia may readily develop, in some of these cases pneumonia cannot be found even on microscopic examination of autopsy material. Pneumonia is not an essential part of the clinical picture and, even if present, requires no modification of treatment.   While the treatment to be outlined for the acute bronchitis is entirely adequate for any associated pneumonia, the reverse is far from true.   The diagnosis and treatment of pneumonia in these cases, and neglect of the special therapy necessary to overcome the extreme anoxia and restore and maintain a clear airway, contribute greatly to the mortality from asphyxia in this disease.

The acute onset of dyspnea, cyanosis and air hunger may suggest other diagnostic possibilities, such as status asthmaticus, acute pulmonary collapse, embolism, spontaneous pneumothorax, acute miliary tuberculosis, lymphatic carcinomatosis of the lung and pleura, or localized laryngeal, tracheal or bronchial obstruction.   These must be excluded.   While roentgen-ray examination is valuable in the differential diagnosis, its use may not be possible in some patients because the necessity for constant oxygen inhalation may make the use of the roentgen-ray machine dangerous.   For this reason it is our policy, when the condition of the patient on admission permits, to have him carried to the x-ray room directly from the ambulance for an emergency chest roentgenogram before he is placed in a hospital bed.

TREATMENT

The immediate aims in the treatment of this diffuse obstructive and suffocative condition are the restoration of adequate oxygenation of the arterial blood and the opening and maintenance of a clear airway as wide and free from bronchial secretions as possible.

Oxygen Administration.   The most urgent necessity in the most severe cases is the administration of oxygen in concentrations as near 100 per cent as possible.   The degree of asphyxia is so great that these high concentrations often must be administered for several successive days.   We have seen no evidence of "oxygen poisoning" in our patients clinically.   Attempts to reduce the concentration of oxygen below 100 per cent by dilution with air, or even with helium in the more asphyxiated patients, often result in immediate increase in dyspnea, cyanosis and restlessness, which are relieved when administration of 100 per cent oxygen is resumed.

The favorable effects of maximal oxygen concentrations in the inspired air are: more complete oxygenation of the arterial blood by the greater transformation of reduced hemoglobin to oxyhemoglobin, and by increase in the physically dissolved oxygen in the plasma; reduction in the accumulated oxygen debt in the tissues, and diminution of pulmonary ventilation as anoxemia lessens.   Reduction in the depth and force of inspiration reduces the pathologically elevated inspiratory negative pressure and its evil consequences.   Slowing of the rate of respiration permits a longer period of expiration so that the pulmonary alveoli can empty more completely, and thus the degree of transient functional emphysema is reduced.

The high concentration of oxygen required cannot be attained by the oxygen tent or nasal catheter.   It is best administered by means of the Barach-Eckman (O.E.M.) or B.L.B. ora-nasal masks.   In some of our cases it has seemed that better results might have been attained by administering 100 per cent oxygen under positive inspiratory and expiratory pressure of 2 to 6 cm. of water by means of the helmet hood apparatus, but this was not available to us.   In acute emergencies, we have occasionally given pure oxygen for short periods of time under positive inspiratory

pressure by means of the anesthesia machine with gentle manual pressure on the rubber collecting bag. Oxygen under positive inspiratory pressure may also be administered for prolonged periods by means of the newer resuscitators.[3, 4] *

Positive pressure of from 1 to 4 cm. of water *during expiration alone* is readily available with the positive pressure modification of the Barach-Eckman mask. It is valuable mainly in treating threatening or actual pulmonary edema, since the positive pressure developed in the alveoli during expiration tends mechanically to squeeze edema fluid back into the alveolar capillaries. The gentle distention of the bronchi during expiration may also be beneficial by promoting retention of oxygen in the pulmonary alveoli during the prolonged expiratory period. This makes more oxygen diffuse into the alveolar capillaries. Because positive pressure hinders the venous return of blood to the heart and consequently reduces the cardiac output, it must not be used at a pressure greater than 1 cm. of water in conditions of shock (systolic pressure below 100 mm. mercury), or if the systolic blood pressure drops more than 10 mm. of mercury during the half-hour immediately after application of the mask. The blood pressure should be determined at 10 minute intervals during this period.

As improvement in the clinical condition occurs, the concentration of oxygen may gradually be lowered. When concentrations below 50 per cent become adequate, administration by nasal catheter or tent may be substituted. Some of the patients who require maximal concentrations of oxygen cannot tolerate the masks, and in these also the tent or catheter must be used. With the catheter in the oropharynx, and the maximum flow of oxygen which can be comfortably tolerated by the patient, 5 to 7 liters per minute, a concentration of 45 to 65 per cent may be attained in the inspired air. We have attempted to raise the concentration of oxygen in the tent by connecting two or three oxygen tanks by means of Y-tubes to the single oxygen inlet tube to the tent, and by using a large rubber sheet under the cotton sheet or mattress to diminish leakage.

Oxygen-helium mixtures are lighter and more diffusible than pure oxygen or oxygen-air mixtures. They may be used with tightly fitting masks or with the positive pressure hood. They are available in tanks of 20 per cent oxygen and 80 per cent helium. By connecting such a tank to another of pure oxygen with a Y-tube, mixtures of any desired proportion may be obtained. In the one severely asphyxiated patient on whom we tried such a mixture, it was not tolerated even in 50 per cent-50 per cent concentration, since nothing less than 100 per cent oxygen could in any way relieve the patient's anoxemia and restlessness.

Carbon dioxide, 2 to 5 per cent and oxygen, 98 to 95 per cent mixtures, have been recommended for intermittent administration, a few breaths at a

---

* Such as the E. & J. Stephenson, Emerson, Kreiselman, Pneumatic Balance Respirator (Burns Model) and other models.

time, to stimulate cough and loosen secretions. The increase in pulmonary ventilation so induced is definitely deleterious, as previously explained. Except in the mildest cases these mixtures probably should not be used.

Humidification of the inspired oxygen is very important in loosening secretions, softening tracheal and bronchial crusts, and aiding expectoration. When oxygen is administered by nasal catheter a humidifier is screwed onto the regulator on the tank so that the oxygen stream bubbles through a column of water and carries a variable amount of water vapor with it. When the masks are used with the injector attachment, the latter may be one-third filled with water, and/or an ounce of water may be placed in the rubber collecting bag, taking care to keep the latter dependent to the mask at all times. For greater humidification of the oxygen tent, wet towels may be laid or hung within the canopy of the tent, the rheostat set at the low position, or part or all of the ice in the cabinet removed, if the higher tent temperature so induced is not objectionable. Mechanical humidifiers for the oxygen tent have been described.[1, 5] * In the very mildest cases, where oxygen is not necessary, steam inhalations may be used.

Aspiration of Secretions. Mechanical aspiration of accumulating tracheal and bronchial secretions is the second urgent necessity in those patients whose cough reflex is weak or absent, whose sensorium is depressed, or who are stuporous or in coma. It is also valuable in the conscious patient when the sputum is so thick and tenacious that severe, prolonged and exhausting coughing is required to bring it up. Postural drainage may be tried, but it is usually neither feasible nor effective in these critically ill patients. In many patients, aspiration is easily accomplished through a urethral catheter gently passed through the nostril or through the mouth over the tongue into the glottis and trachea. As a rule, the passage of the catheter through the nose into the trachea after one or several trials is a matter of little difficulty. Indeed, in some patients the passage of a Levine tube into the stomach is difficult because the tip slides into the glottis rather than into the esophagus. Catheter aspiration of the trachea is distinctly a bedside procedure which can be repeated as frequently as necessary. In many cases the nurse can be taught to do it. Severe acute laryngitis or laryngeal edema is a contra-indication to this procedure and calls for laryngological consultation.

The catheter should be a size 16F, fairly stiff and preferably new. A special aspiration catheter, with the distal end open, is on the market and may be used. The catheter is connected to the long rubber tube leading to the vacuum bottle of an electric suction machine by a glass connecting tube. The suction is tested before each passage of the catheter by sucking water from a glass. Merely moistening the catheter in water is adequate for lubrication. Other lubricants make the catheter slippery and hard to handle. It may be necessary to slightly dorsiflex the head and neck and/or pull the tongue out to facilitate entrance of the catheter into the glottis.

---

* Walton Oxygen Tent "Cold" humidifier manufactured by Walton Laboratories, Inc., Irvington, N. J.

The entrance of the catheter into the glottis is usually signaled in the patient by hollow cough, increase in cyanosis and restlessness, and often transient cessation of respiration due to glottic spasm. Breathing, when resumed, is whistling and stridor-like. In case of doubt as to the proper position of the catheter, its outer end is inserted into a glass of water. If the catheter is in the trachea, bubbles will rise through the water during expiration. The catheter is rapidly inserted as far as possible and suction applied as the catheter is drawn up and back several times until as much secretion as possible is aspirated. Aspiration must be completed rapidly because glottic spasm may be severe. If cyanosis of alarming degree develops before adequate aspiration is accomplished, the catheter should be disconnected from the long suction tube for a period of several breaths, or completely removed, the patient allowed to recover and quiet down, and the procedure repeated if necessary.[6,7] Surprisingly large amounts of mucopurulent material may be withdrawn by this method (figure 1). The medium sized and large râles diminish or disappear completely for a longer or shorter time following aspiration. The cyanosis and dyspnea may temporarily diminish, the widely dilated and fixed pupils of extreme asphyxia contract and respond, and the patient may even awake and speak. In some cases, one or two aspirations may serve to turn the tide in favor of the patient; in others, aspiration may have to be repeated every half-hour to one hour for days. Since the catheter can only reach into the trachea or main bronchi, it seems surprising that so much material can be aspirated by this method. However, the coughing which the irritation of the glottis and carina induces serves to express material from the smaller bronchi and bronchioli into the main bronchi, within reach of the catheter tip. The tenacity and continuity of the sticky sputum which fills the bronchial system probably also serve to drag the secretion from the finer and more distant bronchioles. Occasionally a single large plug strategically placed in the trachea or main bronchus may be the cause of the dyspnea, and its removal produces marked relief.

When glottic spasm is so severe that an alarming reaction results, it may be advisable to anesthetize the pharynx and glottis locally before aspiration is attempted. When aspiration through a nasally passed catheter proves impossible in the occasional case, one should not hesitate to ask help from the otolaryngologist or anesthesiologist, who may be able to pass it with the aid of a laryngoscope. A stiff Magill tube may be passed through the nose or mouth into the trachea and catheter aspiration performed through it, thus avoiding the effect of glottic spasm. In the unconscious patient, the Magill tube occasionally may be left in place for several hours to facilitate aspiration, although this is not always advisable.[8,9]

Occasionally, in spite of repeated and apparently effectual aspiration, the patient may gradually or suddenly become more cyanotic and moribund. Under these conditions, bronchoscopy must be done and the bronchi aspirated under direct vision as thoroughly as possible. Bronchodilator,

vasoconstrictor and antibiotic *mists* may be insufflated through the broncho-scope, but *solutions should not be instilled* into the narrowed bronchi, since asphyxia may result.

When these procedures, once or several times repeated, are obviously ineffective, then tracheotomy becomes the only recourse for the purpose of permitting easy and repeated catheter aspiration of the bronchial tree. The sudden release of expiratory pressure in the bronchial tree induced by the opening in the trachea encourages excessive secretion. A special tra-cheotomy tube which extends some distance outside and beyond the skin should be used, so that some type of expiratory positive pressure device can be attached to prevent pulmonary edema.[10] *   Through this tube a highly humidified oxygen stream, produced by passing oxygen through a nebulizer containing water, can be passed to prevent drying of secretions and crusting in the trachea and bronchi and thus facilitate aspiration.[11]

Bronchodilator and *vasoconstrictor* drugs are administered to shrink the bronchial mucosa and dilate the bronchi to maintain as wide and patent an airway as possible. Aqueous solutions of epinephrine, .5 to 1 c.c. of the 1 per cent concentration or 1 c.c. of 1 per cent neo-synephrine, or mixtures of these, may be placed in a nebulizer of the vaponefrin type and adminis-tered as an aerosol mist through the mouth or tracheotomy tube every two to four hours. The mist is produced by passing an oxygen stream from a separate tank flowing at 4 liters per minute through the nebulizer.[12, 13] Epi-nephrine has both vasoconstrictor and bronchodilator properties, while neo-synephrine is mainly a bronchodilator. Aminophylline and ammonium chloride solutions may also be administered in this way.[14]

Epinephrine in 1 : 1,000 aqueous solution, 0.2 c.c. to 0.6 c.c., or ephedrine sulfate, 0.025 gm. (gr. 3/8) to 0.05 gm. (gr. 3/4), may be given subcu-taneously for the same purpose. Their stimulating action may also be de-sirable. Epinephrine in oil subcutaneously acts for a longer time but must be used with caution. Am'nophylline, 0.24 gm. (gr. 3.75) or 0.48 gm. (gr. 7.5), 10 or 20 c.c. ampules, respectively, may be given intramuscularly, intravenously undiluted, or by slow drip diluted in 1 liter of 5 per cent glucose in normal saline or distilled water.[15]   It is also effective when given as a rectal suppository in 0.5 gm. dosage.

Antibiotic and chemotherapeutic medication is given to overcome the acute infection. It can be initiated as soon as a patent airway and adequate oxygen supply have eliminated the immediate danger of suffocation. If possible, specimens of sputum or bronchial aspirate are obtained for smear and culture and venous blood for culture before such therapy is begun. Therapy need not be delayed, however, until the results of the bacteriologic examinations are known. Organisms isolated on cultures should be tested

* A small O.E.M. mask of the positive pressure type which fits tightly around the tracheotomy opening (and the ordinary tracheotomy tube) and is tied behind the neck is manufactured by the Oxygen Equipment Manufacturing Co., 405 East 62nd Street, New York, N. Y. Humidification is accomplished by filling the injector attachment one-third full of water.

for sensitivity to penicillin, streptomycin and the sulfonamides.   The results
of these tests should determine the choice of drugs.   The organisms usually
found are the common pathogens of the respiratory tract: streptococcus,
staphylococcus, pneumococcus, *Micrococcus catarrhalis,* influenza bacillus,
Friedlander's bacillus and Vincent's spirillum and fusiform bacillus.   Gram-
negative bacilli of the coliform type may be present even in pure culture.
Occasionally no organisms are obtained on smear or culture, at least early
in the course of the acute infection, and a virus etiology is presumed.   Sec-
ondary bacterial invasion soon occurs as a rule even in these cases.   In
general, the gram-positive organisms are more susceptible to penicillin or
sulfonamides and the gram-negative organisms to streptomycin or sulfon-
amides.   Since resistant strains may be present or develop even in species
highly susceptible to a given antibiotic or sulfonamide, the only certain
guides to specific therapy are the sensitivity tests.   Cultures and sensitivity
tests should be repeated periodically during treatment, especially if clinical
improvement is delayed, interrupted by relapse, or does not occur at all,
since the bacterial flora may change and resistant forms appear under the
influence of therapy.   If this occurs, the antibiotic may have to be changed
or the dose increased.

We proceed in a definite routine.   If there is much bronchial secretion,
aspiration is performed thoroughly and is immediately followed by inhalation
of aerosol of epinephrine or neo-synephrine or both.   After a period of five
to 10 minutes, to allow for the maximal shrinking and dilating effect on the
bronchi, a mixture of 50,000 units of penicillin [16, 17] and 50 mg. of strepto-
mycin [18] in 2 c.c. of distilled water or normal saline is administered by
aerosol inhalation.   If culture and sensitivity tests disclose a strain of or-
ganisms sensitive to penicillin or streptomycin alone in pure culture or
predominating, then either antibiotic may be used alone instead of the mix-
ture.   If a strain resistant to both antibiotics but sensitive to a sulfonamide
predominates, then a 3 per cent solution of the sulfonamide in propylene
glycol [19, 20, 21] may be given in the same way.   This is repeated every three
hours.   Propylene glycol used as a solvent for penicillin for aerosol inhala-
tion has been said to potentiate the antiseptic action of the latter.[22]   The
value of detergent solutions such as zephiran (alkyl dimethyl-benzylam-
monium chloride in aqueous solution) or aerosol OT (dioctyl ester of
sodium sulfosuccinate) as solvents for the antibiotics for aerosol adminis-
tration merits further clinical investigation.[23]   By reducing surface tension
and aiding emulsification, they are said to break up pus and cellular detritus
and liquefy viscid mucus, permitting easier clearing of the bronchial tree by
cough or mechanical aspiration and potentiating the action of the antibiotics
by bringing them into more intimate contact with the infecting organ-
isms.[24, 25]   Aerosol inhalation of penicillin dust has been perfected recently
and may prove of value in this condition, although we have had no personal
experience with it as yet.[26]

Parenteral administration of penicillin or streptomycin or both is begun

as soon as the specimens for bacteriologic examination are obtained, without waiting for the laboratory reports.   The initial dose of penicillin is 100,000 units intramuscularly, followed by 50,000 to 100,000 units every three hours day and night.   If fluids are being administered by continuous intravenous drip, the penicillin may be incorporated into this solution.   Streptomycin is given intramuscularly every three hours in divided doses to total 1 to 3 gm. daily.   It cannot be given intravenously.   Sulfadiazine alone or along with the antibiotics may be given the unconscious patient intravenously in 3 to 5 gm. doses twice daily.   To the conscious patient it may be administered orally or by Levine tube in initial dosage of 2 to 4 gm., followed by 0.75 gm. every three hours.   This is preferable to 1 gm. every four hours, since it is best to give all the medications at one time rather than disturb the patient too often.   Alkalinization of the urine may be accomplished by giving Hartman's solution intravenously [27] or sodium bicarbonate or citrate by mouth.[28, 29, 30, 31]   Mixtures of two or three different sulfonamide drugs in the same total dosage, as when only one is used, are said to diminish or prevent precipitation of sulfa crystals and concretions in the renal tubules and prevent the urinary complications so induced, without the necessity for alkalinization of the urine.[32, 33, 34]   Skin rashes and other toxic reactions are, however, more common with such mixtures.[35]

Expectorants liquefy and "loosen" the bronchial secretions so that they can be coughed up or aspirated more easily.   The iodides of sodium or potassium are the most effective.   If the patient cannot take them by mouth in doses of 0.3 to 1.0 c.c. (5 to 15 minims) of the saturated solution in water or milk, three or four times daily, they may be given intravenously in 0.25 gm. to 0.50 gm. doses once or twice daily.

Sedatives may be necessary for the restless patient.   Restlessness increases muscular activity, tissue metabolism and demand for oxygen.   Morphine is usually contraindicated in the *uncontrollably asphyxiated* patient whose vital medullary centers are markedly depressed.   When a patent airway and adequate oxygenation have been attained but the patient remains restless, *very small* doses of morphine may be helpful.   Two to 5 mg. (gr. 1/32 to 1/12) of morphine, especially if given intravenously, may be as effective in these anoxemic patients as the larger doses ordinarily necessary in the nonasphyxiated patient.   Meperidine (demerol) is said not to have a depressant effect on the respiratory center and may therefore be preferable (in small *doses* of 25 to 50 mg.) to morphine.[36]   Other sedatives, such as chloral hydrate, paraldehyde and the barbiturates, may be tried at times but are rarely as valuable as morphine in small doses, preferably given intravenously, or meperidine.   Atropine is not used (because it dries the sputum and makes it more viscid) unless the bronchial secretions are abundant and thin.

The ordering of opiates or other sedatives (because these may be so dangerous if improperly used) must not be left to the inexperienced house staff but must remain the personal responsibility of the attending physician.

The value of the pupillary size and activity as a measure of the degree of asphyxia is largely nullified when opiates are administered, and this may be another serious objection to their use.

Stimulants. Medullary, peripheral vascular and cardiac stimulation may be necessary at times to maintain respiration, circulation and blood pressure. Fundamentally, depression of these functions is due to anoxia of the vital centers in the medulla. It follows that the only effective stimulant is oxygen reaching the medullary centers in adequate concentration, and it alone can completely and permanently restore their function. However, the necessity for the use of certain drug stimulants along with oxygen to tide the patient over a critical respiratory or circulatory crisis will arise. Keeping the blood pressure above the critical level is especially important for the maintenance of renal function.

Among the most effective of these stimulants is caffeine sodium benzoate, 0.48 gm. (gr. 7.5) subcutaneously, intramuscularly or intravenously; coramine (nikethamide), 3 to 5 c.c. of 25 per cent solution intravenously (smaller doses are not effective), and metrazol (pentamethylenetetrazole), 1 to 3 c.c. intravenously. Metrazol is of special importance because it is said to stimulate the carotid chemoreceptors, which take over the control of the circulation and respiration from the nonresponsive medullary centers in state of extreme asphyxia. Carbon dioxide (3 to 5 per cent) by inhalation as a respiratory stimulant has already been discussed. Picrotoxin, although a powerful stimulant in the respiratory depression due to barbiturate or alcohol poisoning, is best avoided in anoxia due to mechanical obstruction. This is so because of the prolonged action of the drug (in contrast to the peak action of metrazol), and its powerful convulsant properties, which might synergize the convulsive tendency already present in the asphyxial state.[37] For peripheral circulatory stimulation, 1 per cent neo-synephrine, 0.3 to 0.5 c.c. intravenously, has a potent but transitory effect in raising blood pressure. Five-tenths to 1 c.c. may be given subcutaneously for a smaller but more prolonged effect. Epinephrine, 0.2 to 0.6 (3 to 10 minims) of a 1:1,000 solution subcutaneously or intravenously, has an evanescent action on heart and blood pressure. Ephedrine, 0.025 to 0.05 gm. (gr. 3/8 to gr. 3/4) subcutaneously, has a more prolonged action but these drugs accelerate the cardiac rate in contrast to neo-synephrine, which slows the rate and increases the contractile power of the heart. In this respect it is preferable to epinephrine and ephedrine. Desoxyephedrine (methedrine), a newer derivative of ephedrine, is very potent. It is given in 10 to 20 mg. doses intravenously and has a more prolonged effect than epinephrine or neo-synephrine. Paredrine (2-((2-methylaminopropyl))-phenol), and amphetamine in the same dosage are also potent. The tendency of these drugs to increase myocardial irritability and cause ventricular ectopic beats, tachycardia and fibrillation in the presence of asphyxia must be kept in mind. Adrenal cortical extract is probably not indicated, and has no value unless special indications, such as acute adrenal hemorrhage, are thought to be

574   L. CARDON, L. LEMBERG, AND R. S. GREENEBAUM

present.   However, it can do no harm, and when the blood pressure drops
to shock levels the temptation to use 30 to 100 c.c. intravenously need not be
strenuously resisted.   Digitalis is given only when congestive failure, auricu-
lar fibrillation or auricular flutter are present.

If the breathing becomes weak and ineffectual, respiration may be main-
tained for long periods of time without effort to the patient with one of the
newer resuscitators mentioned previously.   These will undoubtedly play
an important rôle in the treatment of these cases in the future.   The me-
chanical respirator of the Drinker type should probably not be used for this
purpose because of the deleterious effects of the increased inspiratory negative
pressure which it produces.

Air filters and air-conditioned rooms are of value where asthma due to
inhalants is a prominent part of the clinical picture.

Fluid balance and nutrition must be maintained.   The asphyxiated and
restless patient, even if conscious, cannot eat or drink or does so poorly.
Attempts at feeding often increase restlessness and cyanosis.   Parenteral
administration of fluids is indicated during the acute illness.   Large quan-
tities are not necessary.   The tendency to pulmonary edema must be kept
constantly in mind.   An amount sufficient to maintain a 24 hour urinary
output of 1,000 to 1,500 c.c. should be given.   A retention catheter for the
determination of the urinary output may be inserted.   Two thousand cubic
centimeters of parenteral fluid in 24 hours may be adequate unless the weather
is hot or the patient has fever and perspires profusely.   One thousand cubic
centimeters of 5 per cent dextrose in normal saline, Ringer's or Hartman's
solution may be alternated with a like amount in distilled water and given
by slow drip intravenously or subcutaneously.   The amount and kind of
salts administered depend upon the results of blood chemistry determina-
tions.*   Vitamin B preparations and ascorbic acid may be added.   The
intravenous infusion serves as a simple and convenient avenue for intra-
venous medication which may be incorporated into the fluid or injected
directly into the rubber tubing.   Serum, plasma and blood usually are not
indicated, since collapse and shock in this condition are of central nervous
system origin due to the failure of the medullary centers because of anoxia,
and not due to leakage of water, serum or blood from the vascular system.
However, pooling of blood in the splanchnic areas does occur, and secondary
leakage due to asphyxial increase of capillary permeability may result sooner
or later.   Intravenous administration of serum, plasma or blood may then
serve to restore and maintain blood pressure.   The high incidence of chronic
cor pulmonale in these patients, with the likelihood of the development of

* It is especially important that the high CO_2 combining power which frequently occurs
in this disease be properly interpreted as a compensated gaseous *acidosis.*[38]   The error must
not be made of interpreting the increased sodium bicarbonate in the plasma (unless this has
been noted to develop following excessive vomiting or acute dilatation of the stomach) as
an evidence of "alkalosis" and administering large acidifying doses of ammonium chloride
or dilute hydrochloric acid.   Such a mistake may well prove fatal to the patient.

right heart failure, should temper any tendency to overload the venous circulation with intravenous infusions.

Insulin is essential in the treatment of predisposing uncontrolled diabetes mellitus of any severity. During the acute illness it may be advisable to give regular insulin periodically during the day as dictated by the amount of sugar in the fractional urine specimens. As improvement occurs and the patient resumes a regular diet, the longer acting protamine zinc or globin insulin may be substituted according to indications.

Venesection is indicated when progressive cyanosis is associated with rapidly increasing venous pressure, as shown by engorgement of the jugular veins or by direct venous pressure determinations. Chronic cor pulmonale with right ventricular hypertrophy is present in many of these patients because of their chronic pulmonary disease. The severe anoxemia, marked exhaustion and interference with the circulation of blood in the cardiac chambers, because of the marked variation in intrathoracic pressure induced by attempted hyperventilation through obstructed bronchi and by severe coughing, predispose to rapid right heart failure. The resulting acute increase in pressure of the blood in the right auricle interferes with the drainage of blood from the coronary sinus and accessory coronary veins into the auricle and thereby impedes the coronary circulation. Under these circumstances, the removal of 500 to 750 c.c. of blood by free venesection temporarily improves the coronary circulation and may prolong life until restoration of the airway, adequate oxygenation and rapid digitalization effect permanent improvement in cardiac function and tissue respiration. Cyanosis alone, in the absence of increasing jugular engorgement or measured rise in venous pressure, is not an indication for venesection.

Rest and quiet are essential in these critically ill and asphyxiated patients. Their strength must be conserved. Wakefulness, restlessness and hyperactivity, which increase tissue demands for oxygen, must be combated. Although the exigency of their illness calls for numerous and frequent medical and nursing procedures, the disturbing and irritating effects of these may be minimized by gentle and expert performance and intelligent spacing. As many procedures as can be easily and logically performed together without tiring the patient should be so carried out. The sequence of aspiration and succeeding aerosol inhalations has already been described. Medications should be so spaced that they may all be given at one time, or so close together that the patient need be awakened or disturbed as infrequently as possible, usually every three or four hours. Medications that are not incompatible may be mixed in one syringe, e.g., aqueous penicillin and streptomycin (for intramuscular administration only). Injection of medication through the rubber tubing of an intravenous infusion set spares the patient the discomfort and annoyance of repeated needle punctures and may be done while he is asleep. Undue exposure of body surface should be guarded against. Of course, emergency procedures such as tracheal aspira-

tion must be done as often as necessary without fear of unduly disturbing
the patient.

Nursing.   Intelligent and capable special nurses are essential throughout
the 24 hours, but no nurse should be required to assume complete responsi-
bility for this type of patient.   The unconscious and asphyxiated patient
may be compared to one under a general anesthetic during a surgical opera-
tion.   He requires the *constant personal attention of the attending physician
or a capable assistant throughout the day and night*.   In addition, it may
be advisable to have a laryngologist or physician-anesthesiologist constantly
on call for any emergency procedure requiring their special skill.

It is advantageous to record certain vital information at regular and
frequent intervals, as an anesthetist does during the course of a surgical
operation, to be able to tell the status of the patient at any time at a glance.
The significant findings may be set down in a table:

```
Temperature (graph)
Pulse rate
  rhythm
  strength
Respiratory rate
  strength
  type
Blood pressure
State of asphyxia
  cyanosis
    clinical
    (Oxygen saturation of arterial blood (Milliken oximeter))
    Oxygen saturation of venous blood (direct determination)
  sensorium
    Conscious
    Stuporous
    Comatose
    Response to voice
    Pain sensitivity
  Restlessness
  Muscular twitchings
  Sphincter control
  Pupils
    Dilated, fixed (extreme asphyxia)
    Normal      } less marked asphyxia unless opiates used
    Constricted }
  Corneal reflex
  Other reflexes
    Superficial
    Deep
    Pathologic
  Spasticity or flaccidity
Laboratory reports
  Blood
    Hemoglobin
    Red blood cells
    White blood cells
    Chemistry
      Urea nitrogen
      Glucose
      Chlorides
      CO₂ combining power
    Sedimentation rate
```

COMPLICATIONS

Complications which may be fatal unless anticipated, recognized rapidly and effectively treated include pleural effusion or empyema, spontaneous pneumothorax, massive atelectasis, reflex ileus of stomach or bowel, fecal impaction, acute urinary retention, peripheral venous thrombosis and pulmonary embolism.   Drop of blood pressure to shock levels may precipitate coronary, cerebral, mesenteric or peripheral arterial thrombosis.

Even a small *pleural effusion* may critically reduce the already markedly diminished vital capacity and kill the patient unless it is aspirated early and thoroughly.   In empyema, aspiration is followed by intrapleural instillation of penicillin, 30,000 to 50,000 units, in 5 to 10 c.c. of water or saline or streptomycin, 0.5 to 1.0 gm., or both, daily.

A *spontaneous pneumothorax* of the tension type calls for immediate insertion of a needle into the region of the pneumothorax to liberate the pleural air and reduce intrapleural pressure.   A long rubber tube may be connected to the needle hub and its free end passed into two or three inches of water in a vessel on the floor at the bedside permitting continuous liberation of excess air.   The layer of water acts as a one-way check valve.

Massive atelectasis occurring in spite of frequent bronchial aspiration and not relieved by rolling the patient or thumping the chest when this is feasible calls for immediate bronchoscopic aspiration.

Reflex ileus of the stomach and/or bowel requires gastric aspiration and Wangensteen suction through a Levine tube passed into the stomach. Parenteral administration of saline must be increased under these circumstances and the composition of the infusion more closely guided by the chemical determinations of non-protein-nitrogen, sodium, chloride and CO_2 combining power of the blood.   Enemas, especially of equal parts of milk and molasses, may relieve ileus of the bowel.   Since morphine may contribute to the development of ileus, its use should be avoided entirely or restricted to the necessary minimum.   Prostigmine and other cholinergic drugs and pitressin cannot be used because they may precipitate marked bronchial spasm in patients with an asthmatic propensity.

Fecal impaction is likely to develop in these profoundly ill and inert patients.   Prophylactic treatment includes daily rectal examination, and oil retention and cleansing enemas as necessary.   Mineral oil by mouth is contraindicated unless the patient can swallow because of the danger of aspiration followed by lipoid pneumonia.   Fecal impaction is treated by digitally breaking up and removing the fecal mass and by oil retention enemas.   Unrecognized fecal impaction may be the cause of great restlessness which is mistakenly attributed to the anoxia, does not respond to large doses of sedatives and narcotics, and is relieved only by the discovery and removal of the fecal mass.

Acute urinary retention is fostered by the following factors: (1) general reflex paralytic propensity on a toxic basis; (2) the inhibiting effect on

bladder tone of the sympatheticomimetic drugs used in the treatment of bronchial spasm; (3) the effect of morphine; (4) the presence of prostatic hypertrophy, and (5) the recumbent posture. Use of the cholinergic drugs is contraindicated. The retention catheter must be resorted to. The administration of sulfonamides and antibiotics for the primary disease will tend to prevent the development of cystitis. Like fecal impaction, unrecognized urinary retention may be the cause of violent restlessness which is attributed to the anoxia, does not respond to large doses of sedatives and narcotics, and is relieved only by catheterization of the bladder.

Stasis of venous blood and phlebothrombosis in the lower extremities may be prevented by passive exercise, moving the patient's ankle, knee and hip joints through their full range of motion five or 10 times, and centripetal massage of the main muscle masses of the legs and thighs for three minutes three times daily. The anticoagulants are used only when actual thrombosis or embolism is recognized. Repeated pulmonary embolism may call for ligation of the femoral or iliac vein.

Drug Reactions. While the use of the various medications enumerated may be life saving, the possibility of reactions to some of the drugs remains a constant danger. The patient, if conscious, and the family should be interrogated carefully about previous evidence of sensitivity to any of the drugs whose use is contemplated. Any such history strictly contraindicates the use of that particular drug. The potential irritation and swelling of the pharyngeal and respiratory mucous membrane induced in some patients by iodides or the antibiotics by aerosol inhalation are particularly dangerous and may well be the final straw in precipitating a fatality in these desperately sick patients. The well-known toxic effects of the sulfonamides are more frequent and dangerous in allergic patients In the absence of a definite history of intolerance, the risk must be assumed. If a severe reaction develops, the inciting drug must be discontinued at once. The new antihistamine drugs are valuable in the treatment of these reactions and may permit continuation of the medicament if the reaction is mild or involves a site other than the respiratory mucous membrane.

Summary of Treatment. The treatment here described is the complete regimen as we have used it in the sickest patients, especially those so profoundly asphyxiated that adequate cough and expectoration are absent. In these, repeated mechanical tracheal and bronchial aspiration may make the difference between recovery and death. In other markedly dyspneic patients who can still cough and expectorate but who are exhausted by the effort required, the catheter may be used to aspirate the raised sputum which has been deposited about the laryngeal orifice or in the pharynx. In moderately sick patients, aspiration is not required but the other elements of treatment are the same. They include administration of humidified oxygen, expectorants, bronchodilator, vasoconstrictor, and antibiotic and chemotherapeutic agents by aerosol inhalation, orally and parenterally. In the mildest cases, steam inhalations and expectorants may be sufficient. An

abdominal binder works favorably in some patients by raising the expiratory position of the diaphragm, increasing its respiratory excursion, and aiding expression of bronchial secretion.

The active treatment of the mild and moderately sick patient is the prophylactic treatment of the severely ill patient and may prevent progress of the disease. *The potentialities of even the mildest upper respiratory infection in these patients demand that it be treated seriously and carefully from its very incipience.* If progress is not favorable, early hospitalization for constant observation and drastic treatment is advisable. The physician must insist on this even at the risk of being considered an alarmist.

If the infection gets out of hand and the disease progresses to the state of severe asphyxia, it is a terrifying condition indeed, with an exceedingly high mortality.

The prevention of acute upper respiratory infections in individuals with chronic pulmonary disease is highly desirable but not always attainable. The avoidance of contact with persons with even the mildest "cold" is important. Vaccines are as yet of no great value. Influenza A and B vaccine protects only against the A and B viruses, and the immunity is only partial, of short duration, and helpful only in epidemics of these strains. The danger of allergic reactions to egg protein in the vaccine is present. In winter, the warm and dry, sunny climate found in the southwestern states is definitely beneficial.

CASE REPORTS

Case 1. A 57 year old shoemaker who had worked for years in an atmosphere laden with abrasive dusts was hospitalized October 12, 1945, because of severe dyspnea, wheezing and cyanosis of two days' duration. A "cold" had developed two weeks earlier. He had previously had asthmatic wheezing from time to time. He had been treated intensively for acute left ventricular failure for three days without improvement before he was first seen by L. C. on October 15.

The patient was acutely ill at that time, dyspneic and very cyanotic when out of the oxygen tent, though not especially orthopneic. His temperature was 100° F. pulse rate 120, and respirations 34 per minute. The lungs were hyperresonant, with wheezing and sibilant breath sounds throughout. Showers of moist râles were heard over the right middle lobe. No evidence of acute left ventricular failure was found. Uncontrolled diabetes mellitus was present. The leukocyte count was 18,800 per cu. mm., with 82 per cent neutrophils. The electrocardiogram presented a right heart strain pattern and enlarged P_2 and P_3 compatible with a diagnosis of chronic cor pulmonale. A roentgenogram of the chest revealed marked emphysema and pulmonary fibrosis with bronchiectasis. The heart size and shape were normal.

Acute, diffuse, purulent bronchitis superimposed on chronic pulmonary fibrosis, emphysema and possibly bronchiectasis were diagnosed. The therapy for supposed heart failure was discontinued. The patient was kept in an oxygen tent. Penicillin and later sodium sulfadiazine were given parenterally and potassium iodide orally. The diabetes was controlled by insulin. At 10 p.m. on October 15, the patient had an acute exacerbation of dyspnea and cyanosis, temporarily relieved by venesection and removal of 480 c.c. of blood. Muscular twitchings were present. The patient was very dyspneic and cyanotic the next day in spite of the administration of 95 per cent oxygen with a BLB mask. When the dyspnea and cyanosis became more

marked later in the day, and moist râles appeared bilaterally as high as the spines of the scapulae, the BLB mask was replaced by a positive pressure mask, using 3 cm. water pressure and 95 per cent oxygen. The trachea was aspirated with a catheter attached to an electric suction apparatus, with subsequent marked lessening of the dyspnea and cyanosis. The aspirated purulent material contained *Staphylococcus albus,* beta and gamma hemolytic streptococcus, and *Pseudomonas aeruginosa.*

Bronchoscopy was performed on October 17, with aspiration of mucopurulent secretion from both main bronchi. The patient's condition immediately improved and he continued to do well. The oxygen tent was no longer needed on October 21. The patient was well enough to go home October 31.

The history of a recent upper respiratory infection was of the greatest importance in making the correct diagnosis in this case. The uncontrolled diabetes mellitus probably contributed to the severity of the acute bronchial infection. Accurate diagnosis and properly directed therapy resulted in cure.

Case 2. A 61 year old white male had suffered with chronic bronchitis and asthma most of his life. He was hospitalized July 13, 1946, because of sudden exacerbation of dyspnea and cyanosis the previous day. He was severely ill, thin and markedly cyanotic. Breathing was shallow, with marked activity of the accessory respiratory muscles. The temperature was 101.8° F., pulse 110 and respirations 34 per minute. The blood pressure was 145 mm. Hg systolic and 110 mm. diastolic. The pupils were dilated. The chest was large, with increased anteroposterior diameter. Diffuse sibilant and sonorous râles were heard throughout both lungs, with numerous coarse moist râles scattered bilaterally. The sputum was grossly purulent. Acute suppurative bronchitis, chronic bronchitis and pulmonary emphysema were diagnosed.

Oxygen in high concentration was administered with a mask, with resultant decrease in cyanosis, but labored breathing became worse during the first 24 hours. Muscular twitchings and marked cyanosis were evident when the patient did not receive oxygen. The next morning the patient was critically ill, comatose and very cyanotic, with shallow respirations and coarse moist râles heard in both lungs.

The wheezing had disappeared. The pulse rate rose to 120 per minute. No improvement was obtained from aminophylline given intravenously or epinephrine subcutaneously.

Emergency bronchoscopic aspiration was done (Dr. Jacob Lifschutz), and 150 c.c. of mucopurulent fluid resembling curdled milk were aspirated. The patient was better for a number of hours after the bronchoscopy but suddenly became dyspneic, cyanotic and restless, with obvious air hunger despite the administration of 100 per cent oxygen by mask. Another 150 c.c. of similar mucopurulent material were aspirated through a tracheal catheter (figure 1), with considerable relief of symptoms and signs. A smear from the bronchial aspirate contained numerous polymorphonuclear leukocytes, lymphocytes, eosinophils, gram-positive diplococci and streptococci.

At midnight the patient became comatose; corneal reflexes were absent. Tracheal aspiration was repeated. Oxygen and helium, 50 per cent of each, were given but were not tolerated because a maximal percentage of oxygen was needed. Frequent tracheal aspirations were done throughout the night and early morning but only small amounts of material were now obtained. Bronchoscopic aspiration was repeated at 10 a.m., July 15, but very little secretion was obtained. The smaller bronchi were evidently not being cleared of pus by either the catheter or the bronchoscopic aspirations.

Meanwhile the patient had been receiving epinephrine and neosynephrine aerosol, followed by penicillin aerosol inhalation, neosynephrine, epinephrine, ephedrine and penicillin parenterally, and potassium iodide, digitalis and sulfadiazine orally, as long as he could swallow.

Coma gradually deepened. Respirations became shallower, the blood pressure dropped, the temperature rose, azotemia developed, and the patient died despite vigorous treatment of the asphyxia, anoxemia, infection and shock.

Autopsy. At autopsy the smaller bronchi were filled with pus. The necropsy diagnosis was acute diffuse bilateral purulent bronchiolitis, mild bronchiectasis, severe chronic emphysema, focal pulmonary edema (figure 2), and right ventricular hypertrophy. There were no evidences of pneumonia or heart failure. The anatomic features of this case were classical of this disease.

Fig. 1. Vacuum bottle with about 150 c.c. of thick, purulent secretion aspirated from the trachea and bronchi of case 2 by tracheal catheter. Supernatant fluid is water used to wash the catheter.

Case 3. A male of 61 years whose chief complaint was a chronic cough had suffered with chronic asthmatic bronchitis and emphysema for many years. Just prior to hospitalization on March 22, 1947, he had developed an acute upper respiratory infection. The outstanding physical abnormalities on admission were cyanosis of the lips, an emphysematous chest, many coarse moist râles, scattered asthmatic wheezing, a temperature of 101° F., pulse of 100 and respirations of 30 per minute. A roentgen-ray examination of the chest revealed pulmonary emphysema and fibrosis, probably associated with bilateral bronchiectasis in the bases. *Immediate hospitaliza-*
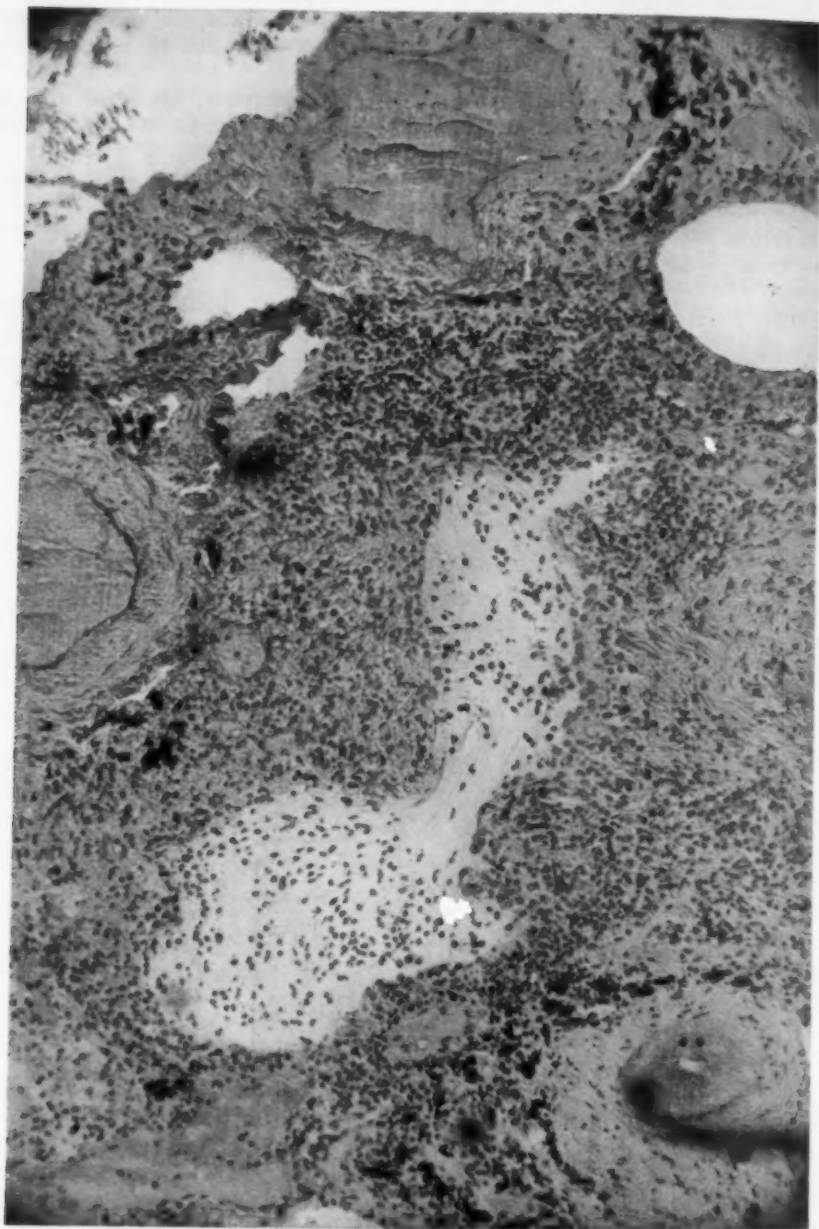
Fig. 2. *Case 2.* Acute suppurative bronchiolitis. Bronchiolar mucosa completely desquamated. Wall of bronchiole densely infiltrated with polymorphonuclear and round cells. Lumen occluded by stringy mucopus. Note associated focal edema, emphysema and acute congestion.

*tion was insisted upon for early drastic treatment, over the protests of the patient
and his family.* Epinephrine, penicillin and streptomycin were administered by
aerosol inhalation. The patient recovered rapidly and was discharged March 29,
1947.

He was rehospitalized on another service November 2, 1947, because of cyanosis,
dyspnea and cough productive of mucopurulent sputum. On this occasion he had
been treated at home by a physician for several days. The physical abnormalities
were similar to those on his first admission. His temperature ranged between 100
and 101° F., the pulse rate between 110 and 140, and the respiratory rate between 24
and 48 per minute. The patient was desperately ill and in coma part of the time
during the ensuing four or five weeks, and then slowly improved. He was treated
with penicillin given intramuscularly, epinephrine and penicillin by aerosol inhalation
and 95 per cent oxygen. Periodically a mixture of 5 per cent carbon dioxide and
95 per cent oxygen was given, and occasionally a mixture of 50 per cent helium and
50 per cent oxygen. Tracheal aspiration of several ounces of mucopus by catheter
passed through a Magill tube inserted by the anesthesiologist was performed a number
of times.

December 13, after the patient had been out of bed several days, he suddenly
became worse, with a return of dyspnea, cyanosis, tachycardia and fever. He died
December 20, 1947. Necropsy was not permitted.

The prompt hospitalization and adequate treatment of the patient's first
attack of purulent obstructive bronchitis prevented progression to the severe
state in which he entered the hospital the second time. He had been sick
at home for several days prior to the second hospitalization, and it is probable
that this delay in definitive treatment contributed to the fatal outcome.

Case 4. A male, aged 69, was hospitalized on another service May 21, 1947,
because of dyspnea, wheezing, gurgling respirations and restlessness. He had suf-
fered with a chronic cough and expectoration for years. He had been digitalized
prior to hospitalization. At the initial examination he was dyspneic and cyanotic
but the jugular veins were not engorged. The chest was emphysematous, with
expiratory wheezes and moist râles throughout both lungs. The liver was not en-
larged. The following day, the patient appeared to be in extremis, with black
cyanosis, gurgling respirations and coma.

At this point a medical resident familiar with the syndrome described here noted
the absence of objective evidence of heart failure and made the correct diagnosis of
obstructive purulent bronchitis. A Magill tube was inserted and tracheobronchial
aspiration performed. Much thick, purulent secretion was removed. The patient
immediately improved and recovered in a few days.

This case demonstrates the importance of accurate diagnosis and the
occasional life-saving value of even a single tracheobronchial aspiration.

Case 5. A 71 year old female had suffered from a chronic productive cough
for years. She developed a "cold" seven days before she was hospitalized on June 8,
1947. She had been digitalized at home. On admission, her respirations were
labored and rapid. The chest was barrel-shaped. The lungs were hyperresonant.
Sibilant and moist râles were heard throughout both lungs, and crepitant râles in
the bases. The acute bronchitis superimposed on chronic bronchitis and emphysema
was immediately treated. Repeated aspirations through a tracheal catheter were done
because she was unable to cough up the obstructing secretions. In spite of the ad-
ministration of oxygen and attempts to clear the airway, she died because of the

Fig. 3. *Case 5.* Section of lung. Bronchial and peribronchial inflammation is evident. Mucus and pus almost occlude the bronchus. Surrounding emphysema.

extent and severity of her pulmonary disease, complicated terminally by bronchopneumonia. Arteriosclerotic heart disease was also present.

Sections of the lung showed a diffuse atrophy of the alveolar walls. Some of the alveoli were collapsed. The bronchi and bronchioli contained pus cells and mucus. The bronchiolar walls were heavily infiltrated with polymorphonuclear cells, round cells and plasma cells (figure 3).

This patient's terminal illness began characteristically with a "cold." Prior to hospitalization, she had been treated exclusively for heart failure. The obstructive bronchial disease had not been recognized and had, therefore, reached an advanced stage before appropriate treatment could be administered.

Case 6. A 74 year old white male had suffered from asthmatic bronchitis for six years, with increasing frequency and severity of attacks. Dyspnea on exertion, marked cough and ankle edema had been observed in the week preceding his hospital admission on another service June 13, 1947. He was gravely ill at the time, with marked dyspnea, cyanosis, orthopnea and jugular vein engorgement. The temperature was 100.2° F., pulse 140 and respirations 50 per minute. The anteroposterior diameter of the chest was increased. Expiration was prolonged. Dullness was elicited over both pulmonary bases; sibilant râles were heard all over the chest and moist râles in the bases. The liver was 8 cm. below the costal margin and tender. Pitting edema of the ankles was present. In spite of the administration of oxygen, digitoxin, aminophylline and venesection with the removal of 350 c.c. of blood, the patient died a few hours after admission.

The lung sections (figure 4) revealed a disruption of the normal architecture, with dilated alveoli and broken intervening septa. Some areas were edematous. Medium-sized and small bronchi were filled with mucopus. The lining epithelium had disappeared in most places and the bronchiolar walls were infiltrated with round cells.

Case 7. This 75 year old white male had complained of mild dyspnea, asthma, chronic cough and expectoration for several years prior to his hospital admission on June 28, 1947. At the initial examination he was dyspneic and cyanotic. His temperature was 99.6° F., pulse 88 and respirations 22 per minute. The chest was barrel-shaped. The lungs were hyperresonant, with wheezes heard throughout and moist râles at the bases. The heart was enlarged. Auricular fibrillation, enlargement of the liver and pitting edema of the lower extremities were present. On June 30 the cyanosis increased, Cheyne-Stokes respirations developed, and the patient became cold and clammy. He died shortly thereafter.

At necropsy, purulent bronchitis (figure 5), chronic emphysema and interstitial fibrosis and bronchiectasis were found, in addition to the enlargement of the right ventricle and acute and chronic passive congestion of the liver.

In cases 6 and 7, congestive heart failure and obstructive, purulent bronchitis and bronchiolitis coexisted. The diagnosis of obstructive bronchitis was overlooked because heart failure was considered an adequate explanation of the patient's serious condition. The treatment of heart failure alone proved inadequate for relief of the obstructive bronchitis.

Case 8. A woman of 73 with a history of long continued chronic bronchitis was hospitalized September 27, 1947, because of dyspnea, cough, expectoration of purulent sputum, a choking sensation and pain in the chest, all of several weeks' duration. She was dyspneic, cyanotic and obviously severely ill. The temperature
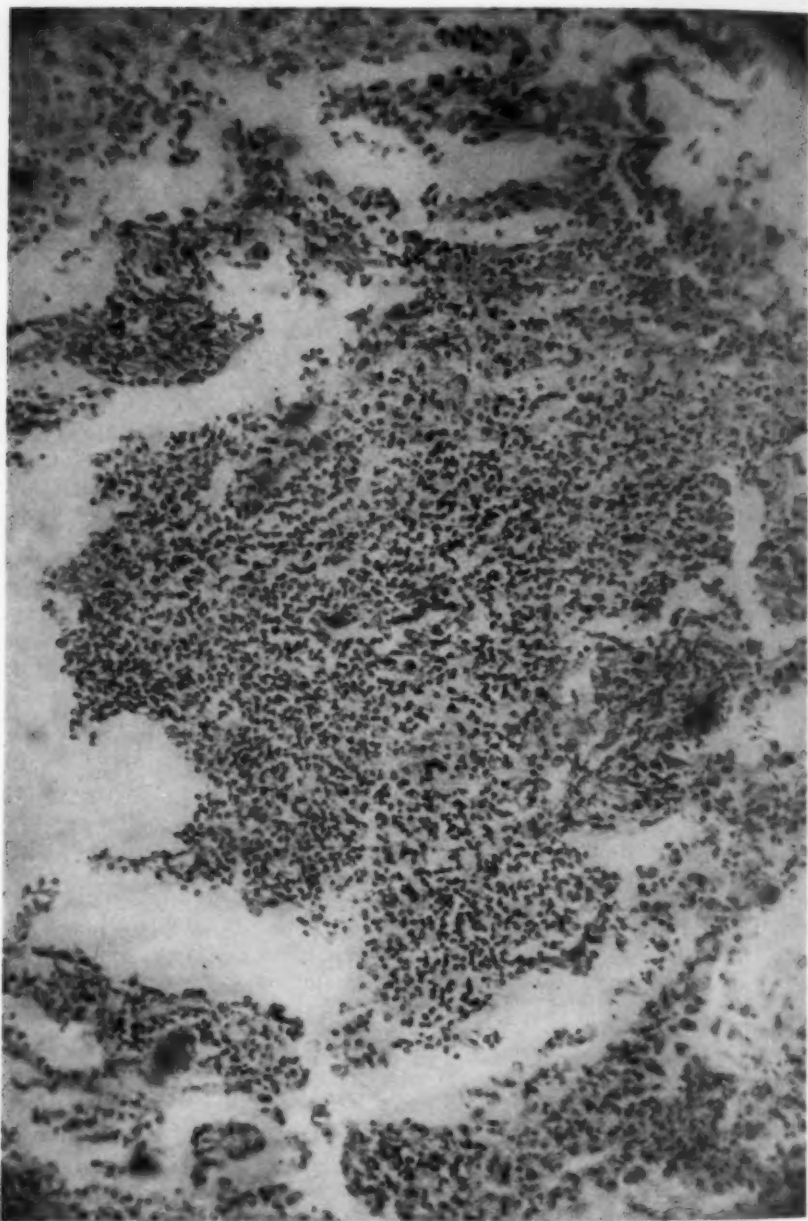
FIG. 4. *Case 6.* Complete desquamation of lining epithelium. Leukocytic infiltration of bronchial wall. Lumen filled with pus. Alveoli dilated. Interalveolar septa broken. Focal pulmonary edema.
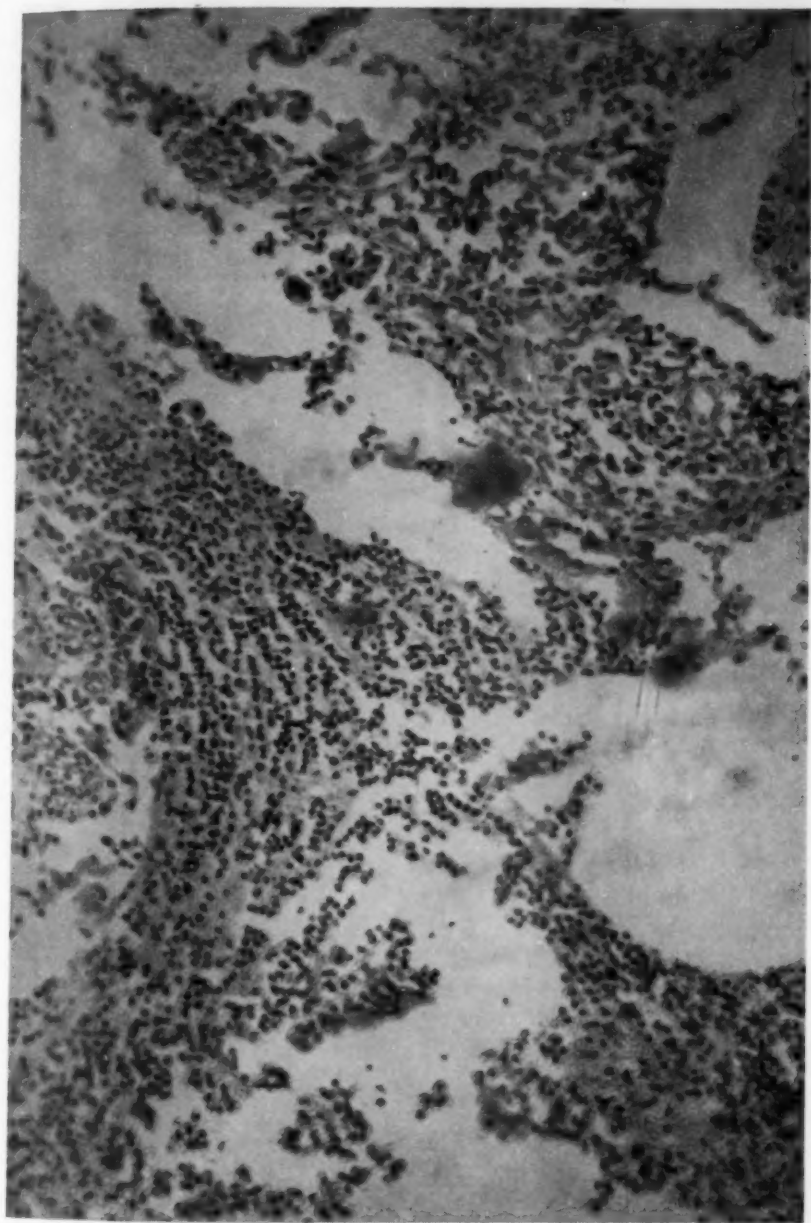
FIG. 5. *Case 6.* High power section showing intense cellular infiltration of bronchial wall.   Severe emphysema.
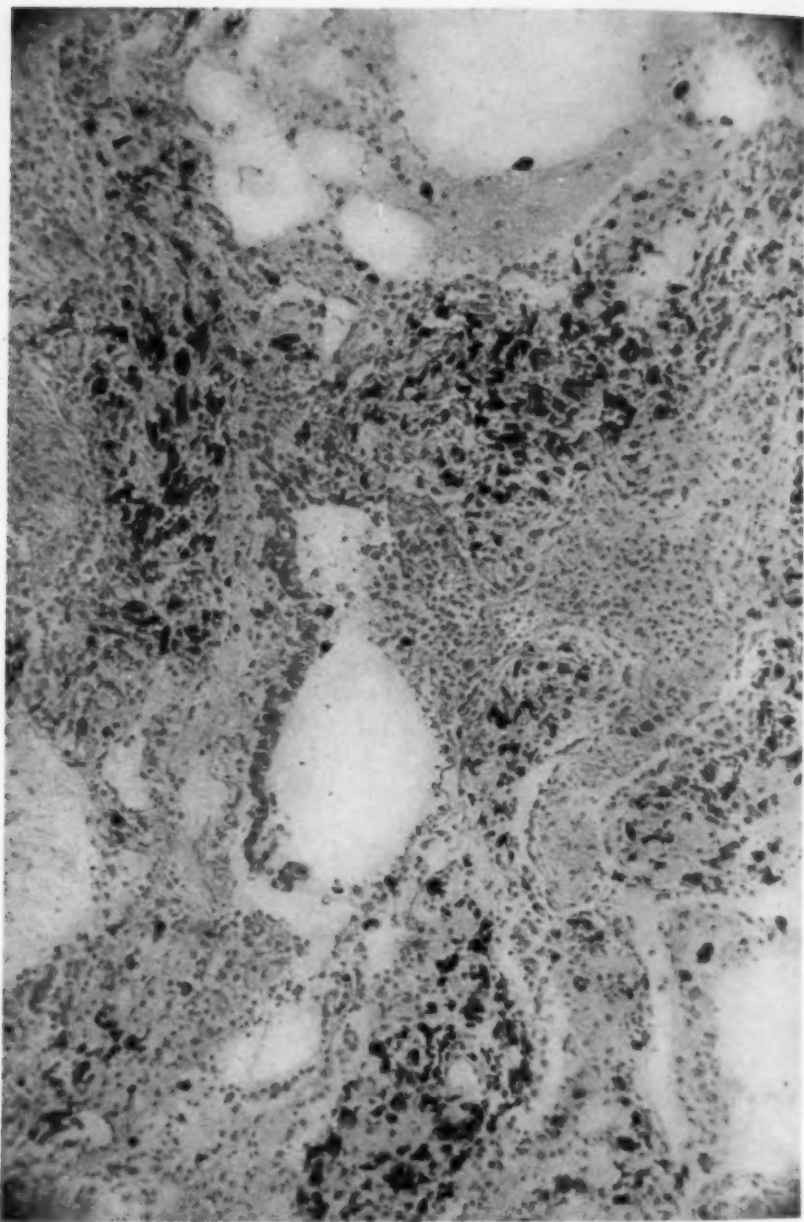
Fig. 6. *Case 7*. Mucopurulent exudate in bronchus. Partial desquamation of bronchial epithelium. Hyalinized, thick peribronchial tissue. Bronchus outlined by coal pigment in peribronchial lymphatics.

was 99.2° F., pulse and respiratory rates 88 and 30 per minute, respectively. The chest was emphysematous, with sibilant and sonorous râles throughout. Her leukocyte count was 14,700, with 72 per cent neutrophils and 11 per cent eosinophils. She was treated with oxygen by mask, penicillin by aerosol inhalation and parenterally, epinephrine and iodides. Within four days the patient was markedly improved, with a slower pulse rate, easier breathing and diminished cough. The sputum became more profuse, with a gradual change from pus to mucus, and the sibilant and sonorous râles disappeared. The patient was well enough to be discharged 13 days after her admission for acute diffuse bronchitis superimposed on chronic bronchitis and emphysema.

This patient did not require tracheobronchial aspiration because she was able to cough up her own secretions.

SUMMARY AND CONCLUSIONS

1. An episode of acute bronchitis ingrafted on chronic asthmatic bronchitis and emphysema, pulmonary fibrosis or bronchiectasis may so obstruct the bronchi that an acute respiratory emergency and death by suffocation may be precipitated.

2. This disease is often misdiagnosed acute left ventricular failure or pneumonia. The consequent delay in proper therapy contributes to the mortality from asphyxia.

3. The essential therapeutic measures are: repeated aspiration of the tracheobronchial tree, administration of oxygen in adequate concentration, and the use of bronchodilator, vasoconstrictor, antibiotic and chemotherapeutic agents. Supportive and stimulant measures and the prevention and treatment of complications are important adjuvants.

4. Even a mild upper respiratory infection in patients with chronic pulmonary disease must be treated seriously from its very incipience. If progress is unfavorable, early hospitalization for constant observation and early drastic treatment is imperative.

5. Residence in a warm, dry climate during the late autumn, winter and early spring is valuable in the prophylaxis of this serious asphyxial disease.

ADDENDUM

Since this paper was presented for publication recent advances have led to some modifications of therapy. The sulfonamides have been almost entirely replaced by the antibiotics, both for systemic and aerosol therapy. The slowly soluble long acting repository penicillins (procaine-penicillin G) in dosages of 300,000 to 600,000 units permit treatment with but one or two intramuscular injections daily. Streptomycin (or dihydrostreptomycin) in doses of 0.5 to 1.0 gram intramuscularly is also given but once or twice daily. The newer antibiotics aureomycin and terramycin which can be given orally, intravenously and by aerosol inhalation have proved to be of great value in the prophylactic and active treatment of this disease. Bacitracin and chloromycetin may be of value in special cases. Isopropyl arterenol, by inhalation or sublingually, has been introduced as a potent bronchodilator. The antihistaminics, variously administered, may be of value under certain circumstances. A new ("weighted bag") apparatus which permits continuous administration of oxygen under positive *inspiratory* pressure is now available (Oxygen Equipment Mfg. Co., New York, N. Y.). Blood sodium and potassium levels are used more routinely in evaluating salt and water balance and replacement therapy requirements and might well be included under Blood

Chemistry in the table. The occurrence of mental symptoms, stupor, coma and death in *chronically* anoxemic patients during treatment with oxygen in high concentration has recently been stressed again.[39] This can hardly modify the indications for as maximal oxygen concentrations as may be necessary (even under positive inspiratory pressure) in the severest cases of *acute* anoxia due to acute diffuse obstructive bronchitis in chronic pulmonary disease. The indications, contraindications and method of tracheobronchial aspiration with a urethral catheter in medical diseases and emergencies have recently been further defined.[40]

BIBLIOGRAPHY

1. Barach, R. L.: Principles and practices of inhalational therapy, 1944, J. B. Lippincott Co., Philadelphia.
2. Unger, L.: Bronchial asthma, 1945, Charles C. Thomas, Springfield, Ill.
3. Motely, H. L., Coumand, A., Werko, L., Dresdale, D. T., Himmelstein, A., and Richards, D. W., Jr.: Positive pressure breathing, J. A. M. A. **137**: 370, 1948.
4. Burns, H. L.: Pneumatic balance resuscitator, Air Surg. Bull. **2**: 306, 1945.
5. Davison, F. W.: Treatment of acute laryngotracheobronchitis, Arch. Otolaryng. **32**: 320, 1940.
6. Haight, C.: Intratracheal suction in the management of postoperative pulmonary complications, Ann. Surg. **107**: 218, 1938.
7. Haight, C., and Ransome, H. K.: Observations on the prevention and treatment of postoperative atelectasis and bronchopneumonia, Ann. Surg. **114**: 243, 1941.
8. Gillespie, N. A. G.: Prolonged use of endotracheal tube, report of a case, Anesthesiology **3**: 217, 1942.
9. Ioreffer, R.: Use of endotracheal tube in therapy of post-traumatic pulmonary secretions, Anesthesiology **7**: 285, 1946.
10. Reference No. 1, p. 279.
11. Albers, C. D.: Use of a nebulizer to produce oxygenated vapor. Report of a case of acute laryngotracheobronchitis, Proc. Staff Meet., Mayo Clin. **18**: 511, 1943.
12. Craeser, J. B., and Rowe, A. H.: Inhalation of epinephrine for relief of asthmatic symptoms, J. Allergy **6**: 415, 1935.
13. Richards, D. W., Jr., Barach, A. L., and Cromwell, H. A.: Use of vaporized bronchodilator solutions in asthma and emphysema, a continuous inhalation method for severe asthmatic states, Am. J. M. Sc. **199**: 225, 1940.
14. Prigal, S. J.: Studies with medicated aerosols—the use of lungs as a portal for the introduction of therapeutic agents for systemic effect, Ann. Int. Med. **28**: 814, 1948.
15. Goodall, R. J., and Unger, L.: Continuous intravenous aminophyllin therapy in status asthmaticus, Ann. Allergy **5**: 196, 1947.
16. Barach, A. L., Silberstein, F. H., Oppenheim, E. T., Hunter, T., and Soroka, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess, preliminary report, Ann. Int. Med. **22**: 485, 1945.
17. Segal, M. S., and Ryder, C. M.: Penicillin aerosolization in the treatment of serious respiratory injections, preliminary report, New England J. Med. **203**: 747, 1945.
18. Olsen, A. M.: Streptomycin aerosol in the treatment of chronic bronchiectasis, preliminary report, Proc. Staff Meet. Mayo Clin. **21**: 53, 1946.
19. Stacey, J. W.: Inhalations of nebulized solutions of sulfonamides in the treatment of bronchiectasis, Dis. of Chest **9**: 303, 1943.
20. Applebaum, I. L.: The treatment of bronchial lesions by inhalation of nebulized solutions of sodium sulfathiazole, Dis. of Chest **10**: 415, 1944.
21. Mietch, N., and Hoskins, H. L.: Inhalation of chemotherapeutic substances, Lancet **2**: 775, 1944.
22. Prigal, S. J., McBovack, T. H., Speer, F. D., and Harris, R.: Aerosol penicillin, J. A. M. A. **134**: 932, 1947.

23. Bryson, V., and Grace, E. J.: Aerosol therapy of respiratory disease, report of 50 cases, New England J. Med. 237: 683, 1947.

24. Petroff, S. A., and Schain, P.: Enhancement of bactericidal properties of well known antiseptics by means of detergents, Quart. Bull. Sea View Hosp. 5: 372, 1940.

25. Palitz, L., and Herman, M.: Treatment of tuberculous and mixed infection empyema with new irrigating solutions, Quart. Bull. Sea View Hosp. 6: 181, 1941.

26. Krasno, L., Karp, M., and Rhoads, P. S.: The inhalation of dust penicillin, Ann. Int. Med. 28: 607, 1948.

27. Gilljan, D. R., Dingall, J. A., 3d, and McDermott, W.: The parenteral use of sodium lactate solution in the prevention of renal complications from parenterally administered sodium sulfadiazine, Ann. Int. Med. 20: 604, 1944.

28. Schwartz, L., Flippin, H. F., Reinhold, J. G., and Domm, A. H.: The effect of alkali on crystalluria from sulfathiazole and sulfadiazine, J. A. M. A. 117: 514, 1941.

29. Climenko, D. R., Barlow, C. W., and Wright, A. W.: Influence of sodium bicarbonate in preventing renal lesions from massive doses of sulfathiazole, Arch. Path. 32: 889, 1941.

30. Fox, D. L., Jr., Jensen, O. J., Jr., and Mudge, B. H.: The prevention of renal obstruction during sulfonamide therapy, J. A. M. A. 121: 1147, 1943.

31. Gilljan, D. R., Garb, S., Wheeler, C., and Plummer, N.: Adjuvant alkali therapy in the prevention of renal complications from sulfadiazine, J. A. M. A. 122: 1160, 1943.

32. Lehr, D.: Inhibition of drug precipitation in the urinary tract by the use of sulfonamide mixtures. I. Sulfathiazole-sulfadiazine mixture, Proc. Soc. Exper. Biol. and Med. 58: 11, 1945.

33. Lehr, D.: The prevention of renal complications by the therapeutic employment of sulfonamid mixtures. I. Sulfathiazole-sulfadiazine mixture, J. Urol. 55: 548, 1946.

34. Flippin, H. G., and Reinhold, J. G.: An evaluation of sulfonamide mixtures and various adjuvants for control of sulfonamide crystalluria, Ann. Int. Med. 25: 433, 1946.

35. Zeller, W. W., Hirsh, H. L., Sweet, L. K., and Dowling, H. F.: Treatment of meningitis with sulfadiazine and sulfamerazine, J. A. M. A. 136: 8, 1948.

36. Barach, A. L.: Comment in Queries and Minor Notes Section, J. A. M. A. 136: 512, 1948.

37. Richards, R. L.: Personal communication.

38. Best, C. H., and Taylor, N. B.: The physiological basis of medical practice, 4th Ed., 1945, Williams and Wilkins Co., Baltimore, p. 108.

39. Comroe, J. H., Jr., Bahnson, E. R., and Coates, E. O., Jr.: Mental changes in chronically anoxemic patients during oxygen therapy, J. A. M. A. 143: 1044–1048 (July 22) 1950.

40. Cardon, L.: Tracheobronchial aspiration with a urethral catheter, J. A. M. A. 142: 1039–1043 (April 8) 1950.

GLOMERULAR LIPIDOSIS IN INTERCAPILLARY GLOMERULOSCLEROSIS *

By S. L. WILENS, *New York, N. Y.*, S. K. ELSTER, *Washington, D. C.*, and J. P. BAKER, *New York, N. Y.*

KIMMELSTIEL and Wilson,[1] in their original description of the lesions of intercapillary glomerulosclerosis, noted the occasional presence of fat in the involved glomeruli. They did not attach any great significance to this finding. Subsequent authors [2, 3, 4, 5, 6, 7] have also made casual reference to glomerular lipid deposits in this condition. Such lipid deposits were apparently considered to be of only incidental interest because they are not always present in intercapillary glomerulosclerosis and because they have been described in a variety of unrelated renal lesions.[8, 9] Simon,[10] however, stressed the frequent occurrence of fatty material in glomeruli that contained the specific lesions of intercapillary glomerulosclerosis and referred to them as lipohyalin deposits. The observation of Rivkind and Leiter [11] that anisotropic lipid droplets in the urine are of diagnostic significance in intercapillary glomerulosclerosis suggests that there may be abnormal renal excretion of fat in this condition.

In several successive instances of intercapillary glomerulosclerosis at necropsy at Bellevue Hospital, New York, inordinately large amounts of glomerular fat were detected on routine examination of the kidneys. It was decided, therefore, to investigate this feature of the lesion in a systematic fashion in order to compare the glomerular lipid deposits of intercapillary glomerulosclerosis with those found in other renal lesions. The object of this study was to discover (1) if a significantly larger amount of glomerular lipid is consistently present, (2) if such deposits occur in a characteristic or specific fashion, and (3) if any pathogenetic significance can be assigned to this finding.

MATERIALS AND METHODS

Frozen sections were prepared and stained by the usual technic with sudan IV from the kidneys of 21 cases in which the diagnosis of intercapillary glomerulosclerosis had been made at necropsy. These included all such cases studied at Bellevue Hospital from 1941 to 1948 in which formalin fixed tissue was available. In no instance was the original protocol diagnosis altered. In each instance, many sections were cut and three from different levels of a single block were selected for staining and permanent mounting in Ferrant's medium. The sections were estimated to range from 10 to 20 micra in thickness.

592

Six control groups of 20 kidneys each that were obtained at necropsy in the same period were examined in identical fashion. These included nonhypertensive diabetics and hypertensive diabetics without renal lesions of intercapillary glomerulosclerosis, and the main varieties of renal disease, as well as one group in which the kidneys were considered to be normal. Many of the pertinent data concerning each group studied are presented in tables 1 and 2.

An attempt was made to estimate the amount of glomerular lipid present in a quantitative fashion. One hundred or more glomeruli in contiguous microscopic fields were graded into (1) those with little or no lipid, (2)

TABLE I

Age, Sex and Race Distribution

Group	Sex		Race		Age (Yrs.)					No. of Cases
	Men	Women	White	Non-White	Under 40	40–49	50–59	60–69	Over 70	
Intercapillary glomerulosclerosis	5	16	15	6	1	3	10	5	2	21
Diabetes and hypertension or arteriolar nephrosclerosis	9	11	17	3*	1	1	5	9	4	20
Arteriolar nephrosclerosis	9	11	19	1	1	7	6	4	2	20
Glomerulonephritis	14	6	17	3	11	3	5	1	0	20
Miscellaneous	13	7	15	5	10	2	2	2	4	20
Diabetes	14	6	18	2	1	3	5	6	5	20
Normal	14	6	17	3	3	1	7	6	3	20
Total	78	63	118	23	28	20	40	33	20	141

* Includes 1 Chinese.

TABLE II

Incidence of Diabetes and Hypertension or Cardiac Hypertrophy

Group	Diabetes	Hypertension*	Cardiac Hypertrophy†	Cardiac Hypertrophy or Hypertension	Diabetes and Cardiac Hypertrophy or Hypertension	No. of Cases
Intercapillary glomerulosclerosis	19	16	17	19	17	21
Diabetes and hypertension or arteriolar nephrosclerosis	20	17	14	18	18	20
Arteriolar nephrosclerosis	0	14	17	17	0	20
Glomerulonephritis	0	11	14	16	0	20
Miscellaneous	0	0	6	6	0	20
Diabetes	20	0	7	7	7	20
Normal	0	1	4	5	0	20
Total	59	59	79	88	42	141

* Systolic 150 mm. Hg and over; diastolic 90 mm. Hg and over.
† Heart weight over 400 gm. in men and over 360 gm. in women.

those with moderate deposits, and (3) those with large accumulations. Glomeruli having a faint diffuse pink hue, as is often the case in completely hyalinized ones, were classified among the first group. Tufts having a few scattered fine granules of sudanophilic material were similarly classified. Glomeruli with a definite diffuse or patchy reddish coloration but without free droplets of fat, and those with many intracellular granules of sudanophilic material, were classified as having moderate deposits. Glomeruli with free globules of fat or with portions of the tuft intensely sudanophilic were considered to have marked deposits. In every instance the fat was examined under polarized light, but only insignificant amounts of anisotropic material were ever detected.

The major defect of this method of estimating glomerular lipid is that sections from a single block are an inadequate sample of the entire kidney, since there is no assurance that fat is deposited uniformly in glomeruli throughout the cortex. This limitation is of considerable consequence in the case of renal lesions that are localized in character. Fortunately, the lesions in which significant amounts of glomerular fat are sometimes detectable proved to be ones that tend to be widely disseminated rather than localized. These included glomerulonephritis, arteriolar nephrosclerosis and intercapillary glomerulosclerosis. Counts made on the three sections prepared from a single block showed, as a rule, less than 10 per cent variation in any one category of glomeruli tabulated. It was believed that this method of differential counting, although at best an arbitrary approximation of the amount of glomerular lipid present in a kidney, is more accurate than a simple qualitative estimation, that it is useful for purposes of comparison, and that each group of 20 kidneys was sufficiently large to control the error of random sampling.

In each case, estimations of the amount of fat in the tubules, interstitium and renal arterioles were also made. The amount of lipid in the first two

TABLE III

Mean Incidence of Glomerular Lipidosis

Group	Marked Lipidosis %	Ratio*	Moderate Lipidosis %	Ratio	No or Slight Lipidosis %	Ratio
Intercapillary glomerulosclerosis	13.7 ± 3.25	—	32.2 ± 3.95	—	54.1 ± 6.31	—
Diabetes and hypertension or arteriolar nephrosclerosis	4.3 ± 1.99	2.6	12.4 ± 2.57	3.5	83.4 ± 4.40	3.8
Arteriolar nephrosclerosis	3.3 ± 0.94	3.1	15.3 ± 3.13	3.4	81.4	—
Glomerulonephritis	3.2 ± 1.24	3.0	12.1 ± 4.20	3.5	84.7	—
Miscellaneous	2.7 ± 1.63	3.1	7.6 ± 2.53	4.4	89.7	—
Diabetes	0.3 ± 0.16	4.1	4.5 ± 1.14	5.4	95.2	—
Normal	0.1 ± 0.07	4.2	4.2 ± 0.80	7.1	95.7	—

* Ratios of difference between means to standard error of this difference (as compared with intercapillary glomerulosclerosis).

of these locations bore no constant relationship to the amount of glomerular lipid. As a rule, kidneys that had heavy deposits of glomerular lipid also had large amounts in the walls of the arterioles; but in many instances, arteriolar lipid deposition was pronounced even when the glomeruli contained none. The amount of arteriolar lipid, in general, was large in cases of hypertension and appeared to be more directly related to blood pressure than to glomerular change. This finding will be reported on in detail elsewhere.
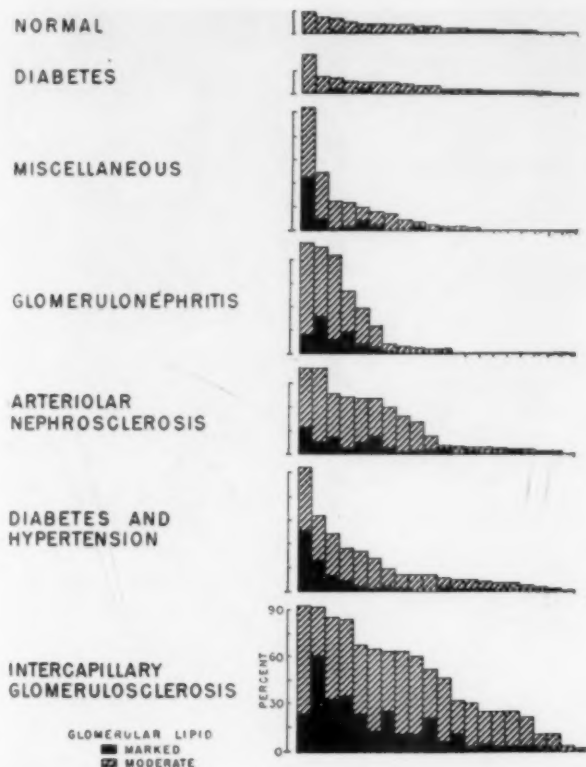

CHART 1. *The incidence of glomerular lipidosis.* Each vertical bar represents the percentage of lipid containing glomeruli in sections of one kidney. For each group these are arranged in sequence according to the percentage of fat containing glomeruli. It will be noted that the highest percentages of glomeruli containing marked or moderate fat deposits were found in the group with intercapillary glomerulosclerosis.

In 95 of the 141 kidneys examined, less than 10 per cent of the glomeruli contained appreciable amounts of lipid. Duplicate counts on some of these showed almost no variation, and on many a single count was deemed sufficient. On the remaining 46 kidneys, counts were done independently by two observers. In 20 of these there was less than 10 per cent variation in any of the categories of glomeruli as classified by fat content, and the average of two determinations was recorded as the final result. In the last

26 kidneys, four counts were done and the average of these was used as the final measurement.

RESULTS

1. *Glomerular Lipid in Intercapillary Glomerulosclerosis.* A higher percentage of glomeruli in kidneys with intercapillary glomerulosclerosis contained lipid than in any other group studied. This difference is statistically significant for each subdivision (table 3). In chart 1, the amounts

CHART 2. *The incidence of glomerular lipidosis.* Kidneys in which more than 40 per cent of the glomeruli contained marked or moderate deposits of fat are shaded; those containing less than this amount are drawn in outline. The preponderance of fat-laden glomeruli in kidneys with intercapillary glomerulosclerosis is evident.

of glomerular lipid found in each group are compared graphically. Each vertical bar represents the percentage of glomeruli containing moderate or marked fat deposits in a single kidney. The kidneys in each group are arranged in sequence according to the amount of glomerular lipid found. It is at once obvious that more kidneys in the intercapillary glomerulosclerosis group contained large amounts of glomerular lipid than those in any other group. In 12 of the 21 cases of intercapillary glomerulosclerosis,

almost one-half or more of the glomeruli contained appreciable amounts of lipid. In none of the other groups did more than three of the kidneys studied contain comparable amounts (chart 2).

Not only did a larger number of kidneys and a higher percentage of glomeruli contain lipid deposits in glomerulosclerosis, but the lipid deposited in individual glomeruli was usually relatively large in amount and often fairly characteristic in distribution. In the kidneys with large amounts of
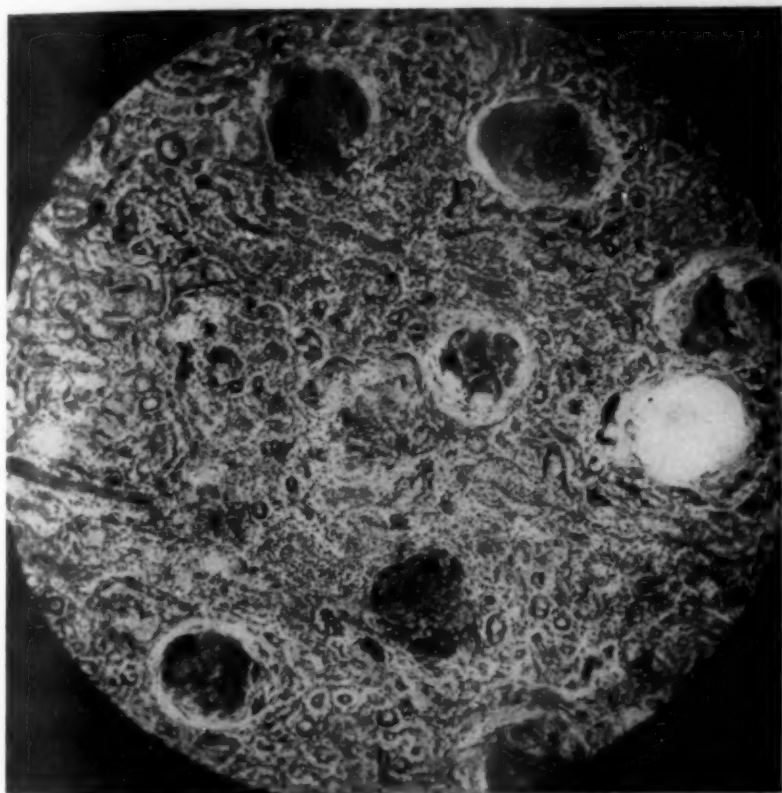

Fig. 1. Renal cortex in intercapillary glomerulosclerosis. All seven glomeruli shown in the field contain large amounts of sudanophilic lipid. Sudan IV stain, × 72.

lipid, many of the tufts were completely filled with fat. This was not observed in any of the control groups. In glomeruli with lesser deposits the fat was often in the form of free globular spheres of the approximate size and location of the hyaline balls that are considered characteristic of this condition. A high percentage of the hyaline spheres contained stainable fat. In fact, it was thought that hyaline spheres might result from gradual transformation into or replacement of fat globules by hyaline connective tissue, since many stages in such a hypothetic conversion could be found.

There were all gradations, from large round droplets of free fat pocketed in spaces apparently between contiguous glomerular capillary loops, to completely hyalinized ball-like structures without any stainable fat. If such a transformation occurs, it is admitted that it must do so at such a slow rate that the mechanism by which fat is altered and gradually replaced is not detectable by histologic study.

The lesions of intercapillary glomerulosclerosis in the 21 kidneys were of all degrees of severity. There were nine kidneys in which the majority
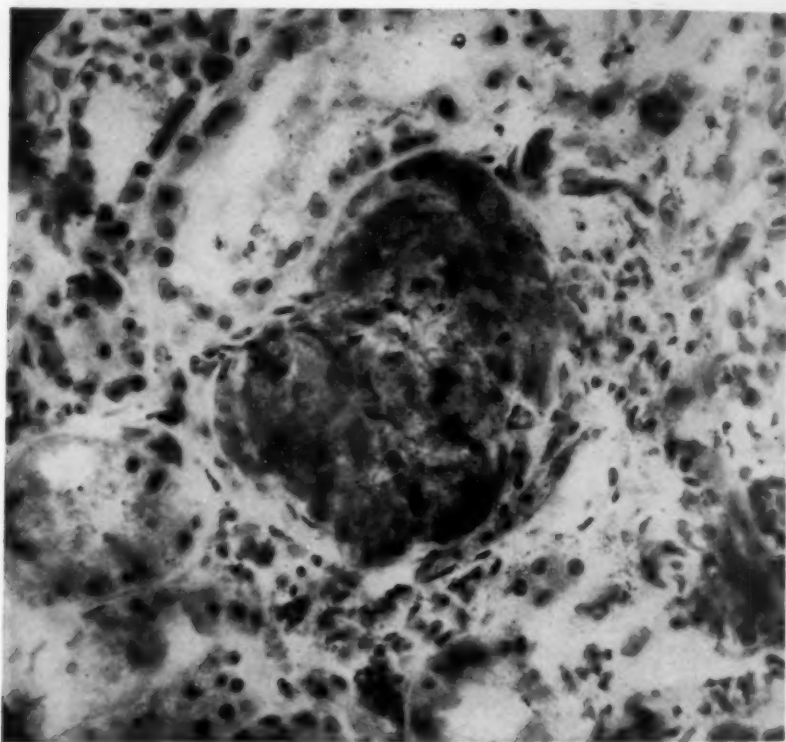

FIG. 2. Glomerulus completely filled with sudanophilic lipid material in intercapillary glomerulosclerosis. Sudan IV stain, × 303.

of the glomeruli had hyaline spheres; in five, the lesions were moderately numerous; in the remaining seven, lesions were found in only a few scattered glomeruli. In general, the amount of glomerular lipid was directly proportional to the number and severity of glomerular lesions. There were only three kidneys with fairly pronounced lesions in which the glomeruli contained very little fat. It is probable that the lesions of this condition develop slowly and persist indefinitely. Failure to demonstrate fat in an occasional case does not exclude the possibility that such deposits may have been present at some earlier stage in the process.

Two cases without diabetes and two without hypertension or cardiac hypertrophy are included among the group with intercapillary glomerulosclerosis. All had mild renal lesions. Only one of these four, a hypertensive without clinically demonstrable diabetes but with hyalinization of the islets of Langerhans, had appreciable deposits of glomerular lipid.

2. *Glomerular Lipid in Hypertensive and Nonhypertensive Diabetics without the Renal Lesion of Intercapillary Glomerulosclerosis.* The deposi-

Fig. 3. Two large globules of lipid within glomerular tuft in intercapillary glomerulosclerosis. Sudan IV stain, × 276.

tion of lipid in glomeruli can hardly be attributed to the diabetic state alone, since only one in 20 diabetics had more than minimal amounts of glomerular fat. Considerably more glomerular lipidosis was observed in the group with both diabetes and hypertension or arteriolar nephrosclerosis, though in only three of the 20 was the amount of lipid comparable to that found in the majority of cases with intercapillary glomerulosclerosis. Review of the original sections suggested that two of these three would have been more

properly classified as examples of intercapillary glomerulosclerosis, with the latter lesion obscured by associated arteriolar nephrosclerosis. In these two cases, spherical masses of free fat were deposited in many glomeruli. These masses were similar to those noted in the group with intercapillary glomerulosclerosis and were not found in any of the other kidneys of this hypertensive diabetic group. As a whole, the lipid deposits in this group had no consistent pattern. Fat was found diffusely impregnated into scarred portions of tufts, just inside Bowman's capsules, in the walls of hyalinized or necrotic intraglomerular capillary loops, or as fine intracellular granules.
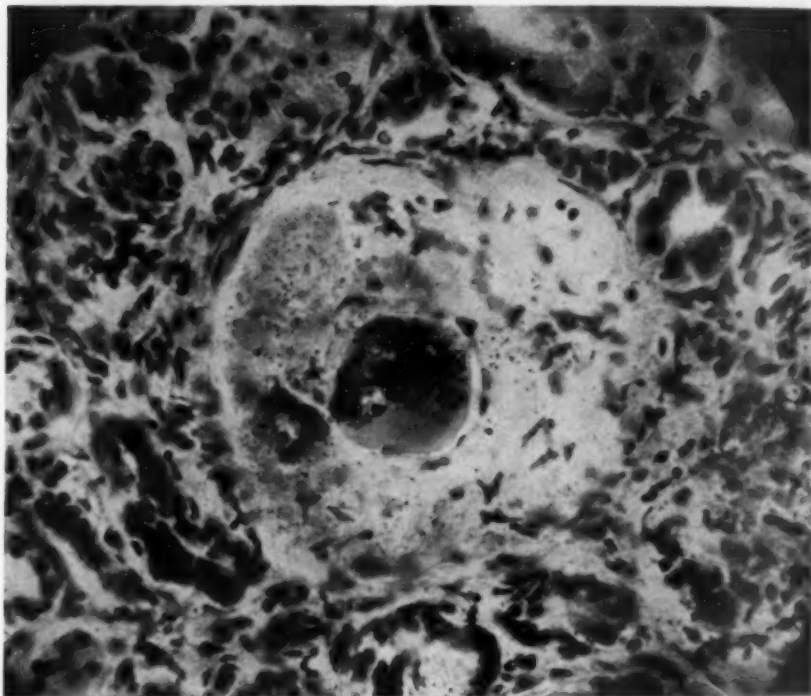
Fig. 4. Hyaline glomerular sphere heavily impregnated with lipid in intercapillary glomerulosclerosis. Sudan IV stain, × 303.

In almost every instance the fat appeared to be mixed with other substances or, when free, appeared as fine droplets.

3. *Glomerular Lipid Deposits in Arteriolar Nephrosclerosis.* More glomerular lipid was found in this group of 20 than in the other control groups. In only two, however, was the amount comparable to that seen in the group with intercapillary glomerulosclerosis. In six others, there were moderate amounts of glomerular lipid. The only distinctive feature of the lipid deposits was its tendency to occur in the walls of capillary loops that had undergone hyaline necrosis. When intraglomerular vascular lesions

were lacking, glomerular lipid was not abundant.   Such lesions were con-
spicuous in five kidneys from younger persons with severe hypertension.
Hyalinized glomeruli were often lightly impregnated with a faintly staining
film of lipid.   Other damaged glomeruli occasionally contained small de-
posits of fat as fine granules, small free droplets, as as a smudgy impregna-
tion into portions of the tuft or capsule.   However, there was no very close
correlation between the severity of the lesion and the amount of fat deposited
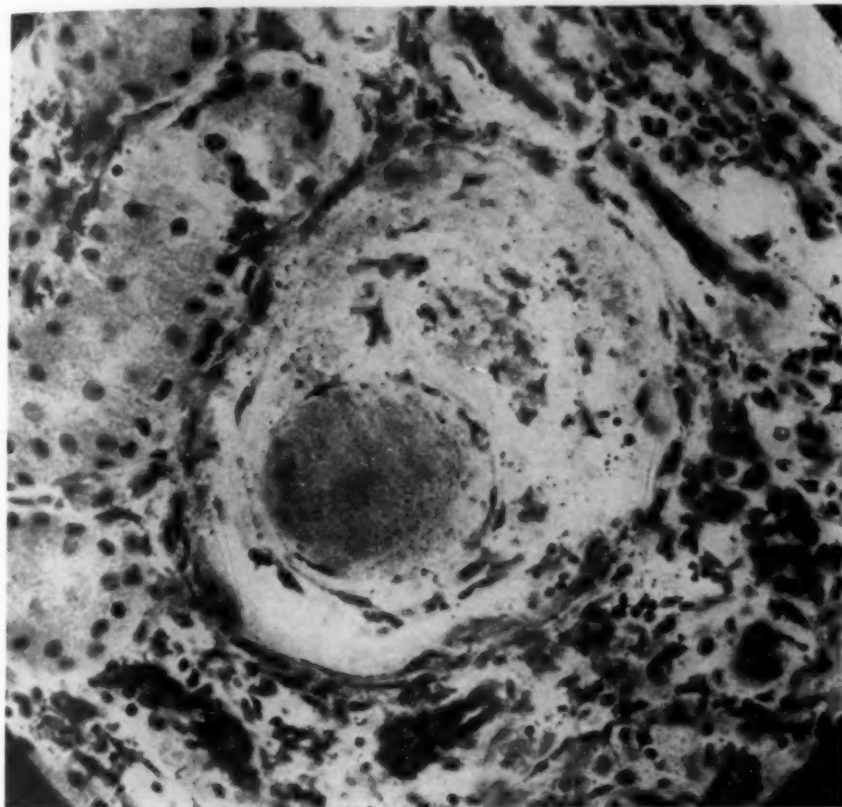
FIG. 5.   Hyaline glomerular sphere lightly impregnated with lipid while remainder of scarred
tuft contains almost none.   Sudan IV stain, × 303.

in glomeruli.   In eight of the 12 kidneys that contained almost no glomeru-
lar fat there were marked atrophy and fibrosis involving both glomeruli and
tubules.

4. *Glomerular Lipid Deposits in Glomerulonephritis.*   In three of the
20 kidneys in this group, all examples of advanced chronic glomerulone-
phritis, there were large amounts of fat in damaged glomeruli.   The fat
was not deposited in any distinctive fashion but resembled in most respects

that seen in damaged glomeruli in kidneys with arteriolar nephrosclerosis, although impregnation into walls of necrotic capillary loops was generally lacking. Ball-like masses of free fat, such as were commonly found in intercapillary glomerulosclerosis, were not observed.

In the other 12 instances of chronic glomerulonephritis in this group, all advanced lesions, nine kidneys contained almost no glomerular fat and three had small to moderate amounts. In the remaining kidneys of this

FIG. 6. Two hyaline spheres in a single tuft. One contains a large amount of lipid and the other almost none. Sudan IV stain, × 276.

group, four of acute and one of subacute glomerulonephritis, there was no stainable fat in the glomeruli.

5. *Glomerular Lipid Deposits in Other Groups of Controls.* The miscellaneous group consisted of six kidneys with amyloidosis, two with Bence-Jones nephrosis, two with lipid nephrosis associated with the nephrotic syndrome, eight with nephrosis of undetermined type, one with chronic pyelonephritis, and one apparently normal kidney from a case of acute and

chronic alcoholism. The group of normal kidneys was obtained from individuals of approximately the same age distribution as the group with intercapillary glomerulosclerosis. Four of these had cardiac hypertrophy, and a fifth, terminal hypertension.

The only subdivision of these two groups that revealed appreciable amounts of glomerular lipid deposition was the one with amyloidosis. One of these had heavy glomerular fat deposits, one had moderate deposits, and the remaining four had light deposits. In each instance, the amyloid itself within the tuft appeared to be impregnated with fat. Further investigation revealed that amyloid in other situations, such as in the spleen and adrenals, is often but not invariably impregnated with fat. Such impregnation may indicate a special affinity of amyloid to absorb lipid, or may be related to hypercholesterolemia that sometimes accompanies the nephrotic syndrome of amyloidosis.

The two cases listed as examples of lipid nephrosis contained no glomerular lipid, although one of these had heavy tubular deposits. One of two examples of Bence-Jones nephrosis had moderate deposits of glomerular lipid. All the other kidneys in this group showed practically no glomerular lipid.

In the group of normal kidneys, none had heavy glomerular deposits of fat although several had very mild deposits. Such deposits were found in either scattered hyalinized glomeruli or in apparently histologically normal tufts.

DISCUSSION·

Glomerular deposits of fat apparently occur as a secondary and inconsistent feature of a variety of renal lesions. There are, however, a number of reasons for believing that glomerular fat accumulations may play a prerequisite rôle in intercapillary glomerulosclerosis, that they may, in fact, represent an early and essential feature of the lesion. In the first place, there is a much more constant relationship between glomerular lipidosis and intercapillary glomerulosclerosis than between glomerular lipidosis and any other renal lesion. Secondly, there is a close correlation between the severity of lesions in intercapillary glomerulosclerosis and the amount of fat found in the glomeruli. No such relationship is demonstrable in other types of renal disease, such as glomerulonephritis and arteriolar nephrosclerosis, in which glomerular lipid deposition is occasionally pronounced but is usually absent even when the lesions are advanced. Finally, there are distinctive features in the pattern of the fat deposition in the glomeruli in intercapillary glomerulosclerosis. In some instances, the entire tuft appears to be saturated with fat; in others, ball-like masses of free fat are lodged between capillary loops. Such deposits have not been found in the other types of renal lesions studied.

To these direct observations may be added some inferences that support the thesis that the lesions of intercapillary glomerulosclerosis may be ini-

tiated as intercapillary deposits of fat. Ordinarily, tufts undergoing hyalinization are reduced in size, but very often tufts that contain hyalin spheres in intercapillary glomerulosclerosis are normal in size or enlarged. This in itself suggests that some material has been deposited in the tuft before hyalinization occurred. It is the size of the tufts that contain hyalin spheres that causes the resemblance in appearance to amyloid deposition noted by Kimmelstiel and Wilson.[1] If one accepts the assumption that the frequent enlargement of the involved glomeruli in intercapillary glomerulosclerosis is due to the original deposition of some abnormal material, then it follows that this material probably is one of high surface tension, such as a fatty mass, since it assumes and retains a spherical shape. The discrete character and sharply delimited margins of the hyaline spheres also support this contention. There are other focal lesions, such as those seen in embolic glomerulonephritis, that are limited to portions of a tuft. None of these, however, has the sharp circumscription of the lesions of intercapillary glomerulosclerosis.

Little is known about the factors concerned with the development of the lesion of intercapillary glomerulosclerosis in persons with both diabetes and hypertension. Only about 50 per cent of such persons have the lesion at necropsy, and in only 25 per cent is the lesion pronounced. Henderson, Sprague and Wagener [12] noted that the lesion was most often encountered in persons in whom the diabetic state had persisted for many years. No such correlation with the severity of diabetes or with the duration or severity of hypertension has been described. Both diabetes and hypertension have their highest incidence of onset at the same period in life—in the middle aged. Both are diseases that have an insidious onset. Few patients can give accurate data as to the time of onset of either disease. Circumstantial evidence can be presented, however, indicating that when diabetes antedates hypertension in any given case, the lesions of intercapillary glomerulosclerosis are more likely to develop than when the reverse is the case.

One bit of evidence is provided by the usual appearance of the kidney in intercapillary glomerulosclerosis: it is seldom contracted, and its decapsulated cortical surface is generally smooth. This suggests that intercapillary glomerulosclerosis does not usually develop in kidneys that are already involved by arteriolar nephrosclerosis. Since the latter lesion is seen most often in protracted hypertension, it follows that the group with intercapillary glomerulosclerosis probably had either mild or relatively short periods of hypertension.

If hypertension and adult diabetes have approximately the same age distribution for time of onset, as is generally believed, then there is an even chance that in any person with both conditions the diabetic state has preceded the onset of hypertension. Thus, in 50 per cent of hypertensive diabetics, diabetes develops initially. This, as already stated, corresponds to the observed incidence of intercapillary glomerulosclerosis in persons

with both of these conditions. This coincidence at least suggests that the approximately 50 per cent incidence of earlier onset of diabetes may be the reason why only about one-half of all hypertensive diabetics develop the specific renal lesion.

If the duration of diabetes is the only important factor in the development of intercapillary glomerulosclerosis, one would expect that the older age group with both diabetes and hypertension would have the lesion. Reference to table 2 discloses that the opposite is true. Fourteen of the diabetic hypertensives with intercapillary glomerulosclerosis, but only seven without the renal lesion, were less than 60 years of age at death. This suggests that the onset of diabetes in the group with intercapillary glomerulosclerosis may have occurred at a relatively young age and further supports the thesis that diabetes may precede hypertension in those persons who develop this lesion.

When the duration of both hypertension and diabetes is stated in reported cases of intercapillary glomerulosclerosis, in most instances diabetes has been the more protracted. For example, in six of seven cases reported by Gould, Stalker and Lyall,[13] the onset of diabetes antedated that of hypertension; the seventh case was one of diabetes without hypertension. Only fragmentary data are available concerning the duration of diabetes or hypertension in the groups studied in the present report. In many instances, these conditions were first detected on hospital admission shortly before death. When a past history of either condition was obtained, only the date at which these were discovered at some earlier medical examination could be provided. Nevertheless, the information available indicates that the lesion of intercapillary glomerulosclerosis is more likely to occur after a prolonged period of diabetes than after a short one and, most probably, in diabetics who subsequently develop hypertension.

Diabetes is known to have been present for an average duration of at least 9.2 years in 13 of the persons with intercapillary glomerulosclerosis; in the diabetic hypertensive group without the renal lesion, the known average duration of diabetes in 12 cases was only 6.1 years. On the other hand, in nine of the persons with intercapillary glomerulosclerosis, hypertension is known to have existed for an average of only 4.6 years. This is approximately one-half the known duration of diabetes in this group. In eight of the diabetic hypertensives without intercapillary glomerulosclerosis, the average known duration of hypertension was 7.1 years, or one year longer than the known duration of diabetes in this group.

The abundant glomerular deposition of lipid in intercapillary glomerulosclerosis is most logically associated with the hyperlipemia of diabetes. Since it was not found in diabetics in the absence of elevated blood pressure, it may be conjectured that in hypertension, conditions within the glomeruli are so altered that lipid is deposited from the circulating blood. Lipid deposition can hardly be attributed to the glomerular damage caused by hypertension, for many cases of severe arteriolar nephrosclerosis were en-

countered in diabetics without unusual fatty change in the glomeruli. It is conceivable that a combination of hyperlipemia and elevated intraglomerular blood pressure might be responsible for the penetration of lipid-containing materials into the intercapillary substance of the tufts. Penetration of lipid substances into the walls of the arteries is probably accelerated in the presence of diabetic hyperlipemia and hypertension. The process that occurs under similar conditions in the glomeruli may be somewhat analogous. Absence of foam cells, cholesterol crystals and anisotropic particles does not necessarily prove that the source of glomerular lipid differs from that of arterial intimal lipid. Secondary changes in lipid deposited from the blood probably occur in the avascular arterial wall that have no counterpart in the richly vascular glomeruli.

There is no proof that the blood pressure within the glomerular capillary loops is elevated in hypertension. It is possible, however, that during the early stages of hypertension there may be transient periods in which elevation of blood pressure is found in the arteriolar capillaries of the glomeruli. Such periods might occur before the afferent arterioles become thickened and tortuous. If elevation of intraglomerular blood pressure is a factor in glomerular lipidosis, the deposits would be most apt to develop in the early phases of hypertension in a person with diabetic hyperlipemia. In persons with protracted hypertension, the afferent glomerular arterioles probably have undergone sufficient elongation and narrowing to prevent elevation of intraglomerular blood pressure. If such persons develop diabetes and hyperlipemia at some subsequent date, the lesions of intercapillary glomerulosclerosis should fail to develop.

Summary and Conclusions

Differential counts of lipid deposits in renal glomeruli reveal that a statistically significant larger amount of fat is found in intercapillary glomerulosclerosis than in any of the other main varieties of renal disease or in diabetic hypertensive persons without intercapillary glomerulosclerosis. Although in a few instances large amounts of glomerular lipid are found in chronic glomerulonephritis, arteriolar nephrosclerosis and amyloidosis, the deposition of fat in these conditions bears no constant relationship to the severity of the renal lesions. In intercapillary glomerulosclerosis, however, the quantity of glomerular fat is directly proportional to the severity of the lesions in most instances. Distinctive features in the amount, form and location of lipid deposits in individual glomeruli are noted in intercapillary glomerulosclerosis. These observations and the inferences drawn from them suggest that the deposition of fat in glomeruli may be of primary importance in the development of the lesions of intercapillary glomerulosclerosis.

BIBLIOGRAPHY

1. Kimmelstiel, P., and Wilson, C.: Intercapillary lesions in the glomeruli of the kidney, Am. J. Path. **12**: 83–98, 1936.

2. Anson, L. J.: Intercapillary glomerulosclerosis, South. M. J. **31**: 1272–1275, 1938.

3. Newburger, R. H., and Peters, J. P.: Intercapillary glomerulosclerosis. A syndrome of diabetes, hypertension and albuminuria, Arch. Int. Med. **64**: 1252–1264, 1939.

4. Derow, H. A., Altschule, M. D., and Schlesinger, M. J.: The syndrome of diabetes mellitus, hypertension and nephrosis, New England J. Med. **221**: 1012–1015, 1939.

5. Allen, H. C.: So-called intercapillary glomerulosclerosis. A lesion associated with diabetes mellitus, Arch. Path. **32**: 33–51, 1941.

6. Porter, W. B., and Walker, H.: The clinical syndrome associated with intercapillary glomerulosclerosis, J. A. M. A. **116**: 459–464, 1941.

7. Laipply, T. C., Eitzen, O., and Dutra, F. R.: Intercapillary glomerulosclerosis, Arch. Int. Med. **74**: 354–364, 1944.

8. Simonds, J. P., and Lange, J. D.: Fatty changes in the glomeruli of the kidneys, Am. J. Path. **17**: 755–765, 1941.

9. Fuller, R. H.: Lipoids in the kidney, Arch. Path. **32**: 556–568, 1941.

10. Simon, M. A.: The nephrotic syndrome with hypertension in diabetes mellitus, Canad. M. A. J. **43**: 425–430, 1940.

11. Rivkind, H., and Leiter, L.: Personal communication.

12. Henderson, L. L., Sprague, R. G., and Wagener, H. P.: Intercapillary glomerulosclerosis, Am. J. Med. **3**: 131–144, 1947.

13. Gould, W. R., Stalker, A. L., and Lyall, A.: Renal complications in diabetes mellitus with special reference to the Kimmelstiel-Wilson lesion, Brit. M. J. **2**: 194–200, 1948.

THE PSYCHOSOMATIC ASPECTS OF CARDIOSPASM *

By John M. McMahon, M.D., Francis I. Braceland, M.D., F.A.C.P.. and Herman J. Moersch, M.D., F.A.C.P., *Rochester, Minnesota*

Introduction

Cardiospasm is a condition the etiology of which has long remained in doubt. The many synonyms which have been used to describe it have usually been chosen in an effort to portray what each investigator believed to be the most descriptive feature. Thus we see such terms as [1] spasm, simple ectasia, atony and idiopathic dilatation of the esophagus, mega-esophagus, hiatal esophagism, functional hiatal stenosis, phrenospasm, preventriculosis and achalasia of the cardia—all pertaining to the same clinical entity.

The purpose of the present work is an assay of the rôle of the responsible psychologic factors in cardiospasm and their relation to the somatic manifestations. Through the years, many clinicians have observed in a considerable number of cases that the initial symptoms have followed incidents of grossly evident psychic trauma. A further relationship of this sort has been indicated by a considerable number of patients who have volunteered the information that their symptoms are usually worse when they are "nervous or upset." They complain that at these times it is frequently impossible to swallow. It has also been observed that, in the absence of such tension factors, patients may experience little or no difficulty in swallowing. The nature of these clinical phenomena and the significance of these observed relations are the raison d'être for this inquiry into the life situation of a group of patients with the symptoms of cardiospasm.

The method of inquiry which is used has been called "psychosomatic." As several authors [2, 3, 4] have pointed out, this mode of approach and evaluation itself subsumes a somewhat heterogeneous group of concepts. According to an early definition,[5] it refers only to a point of view, a guiding principle of thought which applies equally to all illnesses. The psychosomatic concept, according to some, is thus held to mean that, inasmuch as the skein of relationships in a disease process can be of such great order of complexity, it is more accurate to think of the component psychic and somatic factors collectively. Conversely, there are those [6] who employ the psychosomatic concept to explain the clinical picture of those diseases which

they believe to be psychic in origin and somatic in manifestation. These are better called "organ neuroses."

This thesis will adhere to what is felt to be the more conservative psychosomatic hypothesis: that of avoiding the assumption that the etiology of these psychosomatic disorders is one which will be found to lie entirely in the realm of psychologic conflicts and their accompaniments. Rather, it will adduce data with the purpose of exposing the integrative nature of both the psychic and the somatic components of the human organisms. It will avoid drawing cause and effect implications, for the reason that such conclusions can be seen only in a complete matrix of documental relationships. The data will be presented as partial evidence substantiating the contention that knowledge of the psychologic milieu in which these somatic phenomena occur is indispensable for complete understanding of the problem.

The reason for this precaution may not be immediately evident. The discipline of psychiatry and its daughter field, psychosomatic medicine, is largely a terra incognita for the investigator. As has been pointed out, the theory which underlies much of what is clinically evident is admittedly hypothetic. There are significant changes occurring in the basic doctrines as a consequence of ever-widening research in the field. There are also huge gaps in the body of evidence, and it is generally agreed that if progress is to advance on a soundly based methodology there is need for a cautious substantiation of the major contentions. This condition should not be interpreted a priori as bias or unfounded skepticism, for nothing could be farther from the truth. Rather, since the insights are so valuable, there is need of their continued refinement.

REVIEW OF LITERATURE

Historically, Major [7] points out that Thomas Willis in his Pharmaceutice Rationalis, London, 1679, unquestionably described cardiospasm and treated it by devising a whalebone with a button of sponge fastened to it as a bougie. He stated: "Without doubt in this case the mouth of the stomach being always closed, either by a tumour or palsie, nothing could be admitted into the ventricle unless it were violently opened." According to Sturtevant,[8] the first case of idiopathic dilatation of the esophagus was described by Purton in 1821 and the second by Hannay in 1833. In 1876 Zenker and von Ziemssen [9] published a study of the condition and collected data on 17 cases from the literature, calling it "simple ectasia." In 1908 Plummer [10] reported 40 cases from the Mayo Clinic, which had increased to 156 by 1912.[11] Though seen fairly often at the larger medical centers, true cardiospasm is still a rather rare condition in the experience of the average practitioner.

It is not the purpose of this paper to review all of the etiologic hypotheses which have been put forth from time to time. One of us (Moersch [12]) has pointed out that cardiospasm is most likely due to some change in the

neuromuscular mechanism, a statement in agreement with many others and perhaps the majority opinion at the present time.   Rake [13] originally reported two cases of cardiospasm in which microscopic examination of the esophagus post mortem revealed a fibrosis of the ganglia with complete disintegration of the ganglion cells.   In his opinion the degeneration of the plexus, if not a constant cause of achalasia, is at least not infrequent. Lendrum [14] gave further support to this hypothesis when he demonstrated a striking loss or absence of ganglion cells from the myenteric plexus, believed to be primary.   Vinson [15] has not accepted this work as authentic because similar postmortem degenerative changes have been observed in patients who have not had cardiospasm.   Others have felt that these changes were secondary to the dilatation of the esophagus which occurs as the condition progresses.

The work of Knight, [16] however, incriminated the autonomic nervous system, though perhaps not its exact rôle.   He demonstrated in cats that the interdiaphragmatic and intra-abdominal portions of the esophagus function as a true sphincter which is relaxed by the vagus and contracts on sympathetic stimulation.   Bilateral section of the vagi reproduced the complete picture of the condition, but if celiac sympathectomy was performed at the same time, no obstruction resulted.   Knight concluded that the obstruction was due to failure of the vagus to open the cardia, or to spasm, but in either case the integrity of the sympathetics was necessary and sympathectomy was recommended therapeutically.   Later Knight and Adamson [17] reported four cases in which sympathectomy was performed.   In their first case there was complete cure five months postoperatively, and in the other three cases there was improvement of symptoms.   Follow-up studies were made too early to warrant definite conclusions, however.   In other hands the same procedure has not been satisfactory, probably because of difficulties involved in producing a complete sympathetic denervation of the cardia, as pointed out by Mitchell. [18]   Of more recent note is the occasional case of cardiospasm or cardiospasm-like dysphagia which follows vagotomy for peptic ulcer. Such a disturbance is usually transient and self-correcting.

This raises the question whether emotional or psychic trauma could influence or upset this delicate sympathetic-parasympathetic balance at the cardia?   The possibility that emotional factors are present has been recognized by many clinicians.   It is their effector mechanism which has been often debated and still remains to be demonstrated.   For instance, Plummer and Vinson, [19] reporting 301 cases seen at the Mayo Clinic prior to 1921, stated their belief that cardiospasm was not a psychoneurotic manifestation. Winkelstein, [20] on the other hand, stated that in a group of eight cases, psychic factors seemed to be the chief agents in producing the disease and felt that psychotherapy might prove helpful in the treatment of this type of cardiospasm if administered early.

Faulkner [21, 22, 23, 24] has reported extensively on the rôle of psychologic factors in the function of the esophagus.   In 1940 [21] he presented a case of

15 years' duration in which the condition had not responded to either routine dilatation or gastrostomy with retrograde stretching of the cardia. In this patient the cardiospasm was thought to be a consequence of emotional disturbances, and a "cure" followed psychiatric treatment.   Faulkner concluded that cardiospasm is a "disease of the frustrated," and indicated that in his experience it does not occur in happy, contented and well-adjusted persons.   He later [22, 23, 24] presented observations on the production of esophageal spasm in patients during esophagoscopy.   The spasm he witnessed could be increased with demonstrable narrowing or complete closure of the lumen by suggestions which produced "destructive" emotions, such as grief, anger, anxiety, apprehension, fear and "spiritual imprisonment." The opposite response was obtained during the experience of such emotions as "happiness, elation, enthusiasm, contentment and security."   He concluded that disturbing emotional influences are underlying factors in the production of cardiospasm and that, in addition to esophagoscopic treatment, the patient's environment and mental outlook should be improved and emotional reëducation instituted.

Mitchell [25] stated that in clinical experience one cannot but be impressed that the most prominent and consistent factor in these cases is "nervousness and shock."   In his opinion, cardiospasm follows accidents or operations in too high a proportion of cases to be merely coincidental.   Emery,[26] in a review of 34 cases, stated that the most definite impression he obtained was that the psychologic state of the patient strongly influenced the course of the disease and its response to therapy.

Dunbar,[27] in her monograph, "Emotions and Bodily Changes," reviewed some of the literature relevant to this impression.   She quoted Schindler as stating that functional cardiospasm, in his experience, is always a psychogenic organ neurosis which can be treated successfully in its early stages by psychotherapy.   The etiologic psychic disturbance is usually superficial, the first serious dysphagic symptoms appearing after a very specific annoyance, an annoyance that had to be swallowed, that is, usually caused by a superior. Once the disease is entrenched as a conditioned reflex, the picture becomes very serious and the patient suffers acutely with every effort to swallow.   Dunbar also quoted Alkan that the pharynx and esophagus are often the end organs of psychic alteration in the form of globus and cardiospasm, but only in the lower part of the esophagus do these functional disturbances result in a definite organic alteration, that is, in dilatation of the esophagus.   She further quoted Albu, who interpreted cardiospasm as a vagotonic symptom on the basis of neuropathy.   His patients gave as the cause of the disorder some violent psychic excitement, and their frequent relapses occurred almost always under the influence of strong psychic stimuli.   This psychic functional disturbance Albu posited as the cause of lasting anatomic changes in the esophagus.

Marcondes,[28] on the basis of material elicited during the psychoanalysis of several patients with dysphagic phenomena, called attention to the psy-

chologic side of the etiology of cardiospasm.   In his opinion, choking is a "psychically conditioned functional disturbance, the organic consequences of which become irreversible after a certain time."   He substantiated his contention by an analytic interpretation of the basic phenomena.   Bockus [29] stated that there is much clinical evidence to suggest that psychogenic factors may play a significant rôle in the etiology of cardiospasm.   He reported a number of instances in which the first symptom followed profound shock or grief.   He described a patient whom he personally observed with demonstrated cardiospasm and tremendous dilatation of the esophagus.   The original onset of dysphagia occurred immediately after the patient had witnessed her son's electrocution by a "live wire" outside her window.

Patients have been studied from time to time from the psychiatric point of view.[30]   Walsh [31] treated with psychotherapy a patient who had been unable to swallow anything, had failed to respond to hydrostatic dilatations and was being considered for esophagogastrostomy.   A good symptomatic relief was obtained, operation was avoided, and two years later symptoms were minimal.   Walsh did not feel that psychotherapy was prolonged enough to resolve all the conflicts present in this patient, but was most encouraged over the result obtained in a relatively short period.

Probably the most complete study of the relation of the emotions to cardiospasm is that by Weiss.[32]   He reported nine cases which he studied thoroughly.   These patients presented symptoms which arose coincidentally with an emotional conflict, in many instances during puberty, and their early life gave evidence of personality difficulties.   It was his opinion that cardiospasm is a "psychosomatic disorder, an organ neurosis, corresponding to a form of conversion hysteria deeply rooted in the unconscious mental life of the individual."   In a discussion of the treatment he cited the necessity for mechanical dilatation in the established case, but stated that an additional psychic approach is of great help for those patients "who do not tolerate the dilator well," those "who get no benefit from self-treatment," the group in which cardiospasm "tends to recur," or the group "which cannot be cured."

Conn,[33] in a discussion of the psychogenic factors in diseases of digestion, stated that the desire to please and appease everyone is a frequent finding in psychosomatic disorders of the gastrointestinal tract.   It was his observation that patients prefer to give in rather than to argue.   He felt that this attitude is a neurotic pattern of propitiation in which the patient is compelled always to play the diplomat, always to see the other person's point of view, with the result that psychosomatic disturbances make their appearance.   This self-deception of the patient is of particular interest because he has convinced himself that he really is "easy-going" and doing the right thing.   Conn presented a case of cardiospasm which showed the effect of this overwhelming, neurotic sense of duty and how a way of life of the same pattern mentioned previously produced a feeling of marked fatigue, rankling resentments

and a sense of inadequacy which literally wore the patient out, and in Conn's opinion resulted in esophageal spasm. After a period of three months, during which the patient was helped by psychiatric treatment, relaxation of the cardia was shown roentgenologically.

That there is basic disagreement concerning the rôle of the emotions in cardiospasm is apparent from the foregoing review of the literature. Much of this stems from the unilateral approach of the particular author. Likewise, it has been only too apparent to anyone who has taken a detailed psychiatric history that clinical impressions in regard to emotional factors are often grossly misleading. Those patients who on the surface appear to be leading a calm, well-adjusted life often turn out to have the deepest of conflicts. Many a severe depression with accompanying suicidal tendencies has been masked in such a way as to deceive the keenest of clinicians for a considerable period. Because much of what has been written about psychogenic factors in cardiospasm has resulted from clinical impressions, and because there are few comprehensive studies in the literature to date from this point of view, it was felt that a more thorough clinical investigation of the background of a group of patients suffering from the disease was justified. With the disease viewed in this light, it was hoped that much information could be gained in the solution of this complex problem.

THE PSYCHOSOMATIC HISTORY

In any discussion of symptoms it is of paramount importance to know that they represent a subjective expression (interpretation) of an individual patient. His quality as an observer (recorder), his experiential background and his psychologic impartiality are some of the many variables which have to be taken into consideration before giving specific value (meaning) to these expressions.

An inquiry into psychosomatic symptoms requires an exploration of both conscious and unconscious meaning of symptoms to the patient. Not only are the obvious implications of the specific dysfunction important, but also insight has to be gained by the patient into the nature and significance of the underlying psychologic conflict which makes the symbolism necessary. In addition, an awareness of these cryptic meanings makes the symptom (dysfunction) amenable to the influence of therapy.

In obtaining historic data, it is important to elicit not only the gross chronology of events which comprise the life of the patient, but even more so to give proper weight and value to the significance of the event to the patient. The variation in values, the difference in the meaning of events, is the reason why similar life circumstances can have such widely different meanings to different persons. This is also the reason why a disease process as a life experience is reacted to in such a wide variety of ways by people who have strikingly similar pathologic changes as well as psychologic experiences.

As the physician's understanding of the patient develops, it will become apparent that certain of the latter's statements will be taken at face value, others rejected and still others interpreted to mean something else, all in the light of the kind of person he is.   This process is not arbitrary or capricious. It is based on the empiric knowledge of the patient and his values.   In essence, it gives more accurate meaning to the relationships which constitute the patient's life.   In selected cases the use of psychologic tests, such as the Rorschach personality evaluation, may be an important and useful adjunct in this regard.

It is evident that, whereas it would be folly to ignore psychic factors in the evaluation of the patient as a whole, it is clearly inconsistent with the mind-body concept to adduce data which give disproportionate etiologic significance to psychologic factors.   As Braceland and Giffin [34] recently pointed out in a discussion of the mental changes associated with multiple sclerosis, it is well to differentiate between the psychologic milieu in which a disease develops and the process responsible for its development.   For example, tuberculosis may develop amidst filth, squalor, economic depriva- tion and the like, and yet it is well known that these environmental factors merely predispose the patient to vulnerability to the bacterial invader.   This paper, then, is a plea for the evaluation of the total process operative in a patient.

It is at once apparent that a truly definitive analysis requires the establish- ment of the significance of the symptoms or the disease to the patient in question.   It is further true that in any discussion of emotional factors in disease, it is not only the variety of emotions which is important but the way in which these emotions are experienced.   Thus in any study of this nature, a multiplicity of variables has to be considered, especially in view of the widely varying life experiences of each person, as well as the signif- icance of such experiences to the individual in question.   A statistical ap- proach to these problems for the most part tends to obscure rather than to clarify the basic nature of these processes.   The demand for control studies cannot be satisfied, for the obvious reason that patients and their problems are unique.   In order to control any phenomenon accurately, there is need to keep all of the variables constant with the exception of the one under con- sideration.   It is manifestly impossible to control such factors as parental attitudes, specific life experiences, psychologic attitudes, associations, moods, and so forth.   Binger and associates [35] summarized the problem when they pointed out that statistical data concerning human behavior are singularly wanting, and the comparison of an individual's reaction to statistically derived standards may prove unrewarding except within wide frameworks. It is more important to ask the question: How does a patient handle his conflicts and his feelings of anxiety?

To repeat, an understanding of the psychosomatic concept would imply an inevitable bias when any disease is studied from a limited point of view, namely, organic or psychologic.   Though certain diseases *may be* psychic in

origin and somatic in manifestation, not enough information has been accumulated to expose the precise modus operandi by which functional impairment can become structuralized.

METHOD OF STUDY

As soon as the clinical examinations were completed, 25 patients whose diagnosis of cardiospasm had been established were referred to one of us (McMahon) for study. Since these patients remained at the clinic only as long as the routine dilatations were being carried out for symptomatic relief, the period of study was somewhat limited at times. Nevertheless, each patient received a minimum of three interviews, and during the available time every effort was made to secure an adequate psychiatric history and personality inventory, with special emphasis on determining the presence of psychic factors at the initial onset of symptoms. A correlation between the same factors and both exacerbations of symptoms and recurrences of the illness following periods of physical well-being was also sought. The assay of personality features was attempted according to a suggested history outline.[36, 37] No psychotherapy as such was intended as part of this study. However, as the work progressed and experience was gained with some of the facets of the problem, those patients who seemed desirous of help were guided by such superficial interpretations as seemed indicated. It is likewise recognized that ventilation of emotional problems is often in itself of therapeutic benefit. As was briefly mentioned previously and as is becoming increasingly apparent from the case histories and discussion to follow, many of the patients interviewed were fully cognizant of tremendous emotional factors in their illness for considerable periods prior to their coming to the clinic.

RESULTS

A. Analysis of data gathered from the case histories revealed several interesting points worthy of mention. The over-all group was made up of 12 males and 13 females, including one child, aged 12 years. The average age was 41.25 years, with seven patients less than 30 years and four in the seventh decade. Broken down by decades, however, the largest number (eight) was in the fifth decade at the time of examination. Average duration of symptoms prior to the time when the patient was seen at the clinic was slightly more than nine years, with a range of from 10 months to 46 years.

In three of the patients there was a family history of cardiospasm. Oddly enough, in two instances more than one other member of the family was similarly afflicted (father, sister, daughter, mother and brother). An additional patient remarked that her mother choked easily while eating but no diagnosis was ever established. While no definite conclusions can be drawn from the foregoing, the family constellations were such as to suggest

that certain types of reaction pattern had become ingrained in the emotional make-up of the individuals concerned.

A study of the family backgrounds in the group revealed definite evidence of neurotic traits in 17 cases. The latter varied from alcoholism to psychosis. In three additional cases evidence for the same was classified as "suggestive"; for example, "extreme nervousness," or migraine in a parent.

Survey of the childhood of the individual patients considered in this study revealed the presence of early neurotic traits in 22 patients. Included here were enuresis, nailbiting, temper tantrums, phobias, and so forth. Evidently these neurotic traits did not end in childhood, for 23 patients (that is, all but one, if we exclude the single child) manifested other neurotic traits during the adult period. These included depressions, frigidity, inferiority complexes, anxiety states, inordinate masculine drives, inability to accept authority, abnormal dependence on and attachment to a parent, abnormal grief, poor psychosexual development, migraine and duodenal ulcer.

Clinicians who treat patients with cardiospasm have sometimes remarked that as a group they seem unusually well adjusted and easy to manage. The experience of one of us (McMahon) with the cases investigated was exactly the opposite. At the time of the interviews, 18 patients were found to be suffering from varying degrees of depression. In at least two cases the depression was of sufficient depth to cause consideration of hospitalization for electroshock therapy. However, the response to superficial ventilation of the patients' emotional problems, and to supportive therapy in the form of reassurance, encouragement and discussion of problems, warranted postponement of this measure. As will be discussed more fully later in the section on personality structure, these people had never talked over (that is, ventilated) their problems prior to the present interviews, and a definite benefit was noted in practically every case from such ventilation. The duration of this improvement is unknown at the present writing.

It should be noted that the depressed state of the 18 patients in question was masked more often than not, and it was not until after several interviews had taken place that the presence of depression became apparent. In several cases coexisting anxiety states were present.

The following notations were made in other cases: (a) exceptionally hard to approach or establish a good rapport, five patients; (b) overcompensation for small stature, one case; (c) usually flat affect, two cases; (d) overly aggressive behavior, one case.

In the group as a whole, the onset of dysphagic symptoms was found to follow psychic trauma in all but one case. The latter was an exceptionally withdrawn type of individual with whom a good rapport could never be established. It was felt there was much uncovered material, but in all fairness this patient could not be included in the "positive" group.

It was noted in 19 cases that symptoms were always worse when the patient was nervous, upset or under emotional strain. In four other patients

symptoms had remained stationary since the onset, as had the precipitating factors or situation.   One patient failed to note any variation of symptoms with emotional factors and, unfortunately, in a further case this information was not recorded in the history.   In addition, recurrence of symptoms after treatment can be linked as readily to psychic trauma as was the onset of the illness.

B. The following personality factors were found to be common to the group with cardiospasm:

1. These individuals are *perfectionistic, neat, orderly* and *meticulous* about everything that affects their lives: clothes, care of their homes, conduct of business, and so forth.   They detest work done in a sloppy or slovenly manner.   Often they will repeat something many times to get it "just so," though a casual observer might detect no essential change.

2. A majority are energetic, or were so until the onset of their present symptoms.   However, there was a surprising *lack of aggression* in the make-up of all but three patients.   This was often carried to extremes because of the frequent *dependent make-up* of the individual emotionally. Along with this lack of aggressiveness, it was noted that these patients were *unusually submissive.*   They were uniformly and constantly dominated by others, usually a parent, and though they were often aware of this situation, their inability to achieve emotional independence often gave rise to strong feelings of frustration and resentment.

3. Most patients with cardiospasm are unusually *sensitive* and *easily offended.*   Once offended, they seem unable to forgive, and *harbor resentment* for long periods.   For instance, the patient in case 17 had not spoken to a brother for many years because of certain incidents in their childhood.

4. They are *shy* and *bashful* and often have *strong feelings of inadequacy.* As a group they were generally *hard to approach,* and for this reason they had few close friends.   If perchance this outer barrier could be broken, however, the friendships formed were likely to be strong and enduring.

5. They keep their *feelings to themselves,* and seldom does anyone know their true reaction to a situation; as one patient expressed it: "When I get upset, I just swallow my anger and say nothing."   Often this was blamed on the lack of an understanding, sympathetic person in the home (generally husband or wife) with whom they could talk over their problems.   Many of the patients commented that they had never unburdened their pent-up feelings until they visited the clinic.   It was further noted that they generally avoid sympathy and, on occasion, will go to extremes to keep from having their condition known and sympathy expressed.

6. *They like to be well thought of:* in fact this seemed almost a basic need of the personality.   To accomplish this in part they will avoid frankness in their dealings with others.   Instead, an evasive remark will be made to conceal their true feelings.   They will go to extremes to *avoid arguments,*

especially with a mate. Even when this is impossible, they will seldom present their side of the dispute, preferring to remain silent.

It will become at once obvious that many of the foregoing personality factors are common to several conditions considered psychosomatic; namely, essential hypertension, migraine, peptic ulcer, and so forth. The question is often asked why the somatic reaction to psychic trauma varied from individual to individual, that is, why should one person react by development of a disturbance of the cardiovascular system and the next by an alteration in gastrointestinal function. The answer to this question is by no means easy and has not been solved at the present writing, although Adler and others have spoken of organ inferiority and the choice of neurosis. Several interesting facts were noted during this study, however, which might shed some light on the problem: For instance, case 17 demonstrates how important was food in the patient's early life. As a young Jewish lad attending high school in Poland, the patient had frequently been attacked by rabid anti-Semitic schoolmates who stuffed forbidden pork into his mouth. Following this he would vomit and find himself unable to eat for long periods. Later, deprivation of food during World War I and arrest by German Army authorities for possessing a bag of corn meal served to emphasize the importance of food, and might have been factors conditioning this patient in his emotional attitude toward food and method of reacting to environmental stress.

In those cases in which other members of the family were afflicted, environmental factors could have been important in conditioning the patient's particular type of reaction. This evidence is purely suggestive, however, and from it no definite conclusions can be drawn at present.

The following are two illustrative cases, chosen as typical of the group of 25 studied:

CASE REPORTS

Case 2. A white man, aged 64 years, came to the clinic in February, 1947, with chief complaints of dysphagia and regurgitation of food of 16 years' duration. Clinical and roentgenologic examinations revealed the presence of cardiospasm. The family history revealed that the patient was the second of four children and that his mother apparently had suffered from migraine headaches for many years. One sister was characterized as "nervous and fussy." His father was a farmer and the patient grew up in an apparently happy rural environment.

As a child he remembered that his parents were quite strict, that he was afraid of the dark and suffered from enuresis until the age of 15 years. He also had frequent dizzy spells which were relieved by lying down. There were no schools in the vicinity of his home until he reached 12 years, and his education began then, with completion of the eighth grade at the age of 19 or 20 years. From that age until 15 years ago he suffered from "sick headaches," which came on approximately every two or three weeks and were apparently migrainous in nature.

Until the age of 17 or 18 years he had helped his father on the farm. At this time he became apprenticed to a veterinarian for two years, liked the work, obtained his license and desired to make this profession a career. His father had also done veterinary work from time to time, which apparently stimulated the patient's in-

clinations in this direction. Until he was married at the age of 24 years (about 1907), he did veterinary work, part or full time, but after marriage his wife persuaded him to become a farmer instead, because she did not want him gone from home for such long periods as veterinary work would demand. Consequently, in 1908 he started farming in a rather arid region but was unsuccessful and, despite hard work, was in debt constantly from 1909 to 1940. Between 1923 and 1930 his crops were always poor, and something like a drought or dust storm always came along to keep him "in the hole" financially. In fact he remarked that things had always gone against him financially since he had grown up, and he wondered if things would ever "break" for him. The crops were good in 1930 but prices were so low that he was unable to make a profit, and at that time he went about $2,500 into debt.

In 1931 his farm was hit by a plague of grasshoppers, the entire crop was destroyed and he lost everything. As a result, his financial problems mounted and he had to sell all of his stock to help pay his debts. Cattle brought only $20.00 a head at that time, and he stated that this entire shock was "more than I could swallow." His difficulty in swallowing began at this time and, in addition to this beginning dysphagia, he became quite depressed and discouraged. The following year, 1932, while planting the spring crops, he cut his left hand on a buzz saw and was disabled until the fall of 1933. He considered this latter blow the "climax," for it was hard to believe that anyone could have so much bad luck. While on the way to the hospital, the doctors told him that he would probably lose two fingers on the injured hand, and he was faced with the unpleasant prospect of being laid up for a long time without income. It is interesting to note that he could not swallow the first meal which was brought to him in the hospital following this accident, and the symptoms of dysphagia and regurgitation have persisted from that time until the present.

In 1933, after his hand had healed, he and his wife were forced to go "on relief" because of the depression and continued poor crops. This was a bad blow to his pride, which was only offset by the fact that almost everyone else in the neighborhood was in the same circumstance. They remained on the farm until 1934 but "did not raise anything," and finally the patient had to go back to veterinary work. Their farm was lost and they moved to town, but it was two years before they obtained a permanent home and seven years before they were out of debt.

His symptoms have been much the same since the onset, and the cardia has been dilated many times without relief, including 50 dilatations in 1944 alone. There have been no periods of freedom from symptoms, so that he cannot tell the relation to nervousness except that the only meal of the day that he had been able to eat prior to coming to the clinic was in the evening, when he was at home and could relax. There was a maximal loss of weight of 60 pounds (about 27 kg.), largely in the previous five years. Between 1931 and 1935 he was chronically depressed. At the time he was seen he was back in veterinary work and said that he was doing well, "had his head above water" financially and was well thought of in the community. There had apparently been considerable resentment toward his wife for forcing him to give up his veterinary work when they were married and take up farming, which he did not like.

Summary. This farmer, aged 64 years, was forced, at his wife's insistence, to give up the career of his choosing and enter farming, which he detested and at which he was always a failure. The crowning blows, which were more than he could "swallow," occurred when his crops were wiped out by a plague of grasshoppers and when he injured his hand.

Case 14. The patient was a housewife, aged 34 years, who came to the clinic in April, 1947, with the chief complaints of difficulty in swallowing of 16 years' duration and swollen, painful joints for one year. Clinical and roentgenologic

examination confirmed the diagnoses of cardiospasm and rheumatoid arthritis. Her family history revealed that there had been many neurotics and alcoholics on both sides of the family, and the patient had never cultivated her relatives for this reason, calling them "shanty Irish."

Her parents had married at an early age and "never seemed to feel the responsibility of marriage." There was constant fighting and bickering, and her mother was very jealous and her father was alcoholic. There was one other child, an older brother now married. The patient always felt rejected and as long as she could remember was "raised by the hired help." She stated that she sucked her thumb until she was three years old and was whipped for this. She remembered being afraid of the dark and, whenever she did anything bad, was frightened and put in a dark closet. Her mother was very strict and the patient got many "lickings," which humiliated her terribly. Some of them were administered because of her temper tantrums, and many because of enuresis, which lasted until she was 13 years old. (She still had nocturia three times nightly, which she felt was on a nervous basis and a carry-over from this childhood experience.)

Her parents were divorced when she was seven years old, and the patient was put into a boarding school by her mother, in whose custody she was placed. At school she felt that she was given too many responsibilities and had to work too hard, doing many menial tasks besides her studies. In general, she felt that everyone was mean to her, and even her mother never seemed interested in her or her brother. While she was in school, she always wondered why she was a child of divorce and had no home to go to, and on this basis constantly compared herself with other children. Because of these factors, there was a constant feeling of insecurity and, as she summed it up, "There was nothing to look forward to." Her husband stated that this feeling of insecurity was still present, and tells her that she is "afraid of everything."

When she finished high school, she wanted to study nursing and applied to a school of nursing, where she was accepted. When her mother heard of this she would have none of it and, instead, forced the patient into a teaching career against her will. Consequently, she was sent to a college, an event which stirred up terrific feelings of frustration, resentment and rebellion against her mother because the latter would not allow her to shape her own future. As her mother was poor, she was forced to put herself through school. The only way of doing this was to become the "seeing eye" of a blind girl. In return for this service the latter's family paid her way through school. This was an extremely heavy burden, since she had been told by the blind girl's family that she was responsible for both the grades and the general care of her infirm companion. The blind girl was very demanding, confining the patient to her side all day long without interruption. The patient had to arrange "dates" and read the lessons aloud and was never able to relax or have even a few minutes to herself. In addition, the other students, "daughters of spoiled rich," were all snobbish and looked down upon her as a servant. This situation fostered a terrific amount of anxiety and resentment toward her mother for forcing her into a teaching career against her will, as well as toward her position as a virtual servant. These feelings gradually increased, and with them her first symptoms of cardiospasm appeared. Nevertheless, she worked hard and was graduated from college cum laude at the age of 20 years, her symptoms notwithstanding.

Her first job after graduation was as principal of a high school. Here again she felt that there was too much responsibility, and she remembered taking her problems home to bed with her and lying awake thinking about them. She stated that there was continuous anxiety and resentment toward her job, but she had to accept the situation. During this period the dysphagia was much worse and she lost weight. She again thought of giving up teaching and studying nursing, but soon

gave up the idea because she was afraid not only of what people would say but also of her mother's reaction.

Then her esophagus was dilated for the first time, with considerable relief, and there were periods when she could swallow fairly well. However, about every three or four weeks there would be a terrific argument with her mother, with whom she was living. After each of these her cardia would tighten up for one to two days, until she got over her resentment. Every time she was emotionally upset food would stick, but when she was calm it would go down without difficulty. After the dilatation she determined to better herself, so she took postgraduate work and won her Master of Arts degree, specializing in teaching reading to retarded children. She was immediately assigned to large classes in this new field, and when the children did not seem to progress she was quite upset. During this entire period her mother did not want her to marry, go out on "dates," or even have friends of either sex. When fellow teachers would come to her house and make plans to go downtown shopping, her mother would absolutely forbid her participation, so that she was unable to join their groups. She characterized her mother as determined, domineering and selfish, a person who "wanted me to devote all my time to her and possessed me completely in a smothering way." In 1940, when the patient fractured a vertebra, her mother forced her to resume teaching shortly after the cast was removed and long before she felt physically able to work. The patient stated that she never asserted herself in such matters as having friends. Instead, she gave in to her mother and said nothing in order to avoid fights which might extend over an entire week.

About December, 1945, a young man whom she had been seeing without her mother's knowledge proposed marriage. Her mother immediately tried to prevent this by hysterical outbursts, creating scenes, withholding letters from the boy, and so on. The patient was equally determined she would marry and free herself from this situation. When she finally decided to do so, in June, 1946, she gave up her job and started to plan for the wedding. Her mother gave her no peace and, following one "terrible scene," the patient was unable to swallow for an entire week. At the same time, symptoms of rheumatoid arthritis made their appearance, though the diagnosis was not confirmed until later. When she got over this upsetting episode, she had no trouble from either condition until after her marriage.

It should be inserted here that the patient's attitudes toward sex were very immature. She had never received any sexual instruction and always felt embarrassed at the time of the menses, especially after marriage. Any discussion of sex was taboo, and even in college the chapter on reproduction in the physiology text had been removed by the school authorities prior to purchase. Consequently, she always thought that sex and intercourse were horrible and unnatural and that men were "monsters on the prowl." Her mother discouraged any boy friends, and when she did go out the patient was always on the defensive.

However, she was finally married in June, 1946, and, after the honeymoon, she and her husband were forced to live with his family for four and one-half months because of inability to obtain other living quarters. She stated that her husband was kind and considerate, but during the first week or two of her marriage she dreaded intercourse. This repugnance passed off somewhat and she thinks that she had an occasional orgasm, though a good sexual adjustment had not been attained. Her doctor had discouraged pregnancy because of her cardiospasm. During the period when she was living with her in-laws she received daily letters from her mother trying to frighten her into leaving the husband and to make her feel dissatisfied and dependent. Her mother constantly pointed out the folly of her marriage and emphasized what she had given up. Her husband was continually criticized with

unbridled feelings of hatred as the "monster" who had walked in and stolen her daughter.

The patient stated that living with her husband's family was a strain but nothing compared to receiving those letters. The latter likewise infuriated her husband and thus were a constant source of friction between them, which made her extremely nervous and unable to sleep at night. There were other difficulties in adjusting to the marriage. Previously, she had been independent insofar as she had her own source of income. Now she had to get along on her husband's salary, a fact which she resented. She would compare her routine as a housewife with her life as a teacher and wonder if she should have got married, though she had always resented teaching as well.

In the midst of this, about one month after her marriage, the dysphagia and arthritis returned. The patient stated that all three were simultaneous—dysphagia, arthritis and the problem she faced on her return from her honeymoon—and she believed that the latter was responsible for her swallowing difficulty. Since that time her cardia and joints have bothered her only when she is upset. In addition, her menses stopped for five months and she thought she was pregnant. When her mother learned of the latter, she frightened the patient terribly by saying that she could never carry a child to term and would surely die. To make matters worse, in February, 1947, her mother decided to come and live with them. She immediately upset the household, criticized both of them, insulted the husband, and even packed the patient's clothes to take her away from the spouse. The mother stayed 10 days, at the end of which time the patient, feeling that she could tolerate this no longer for her own and her husband's happiness, made her mother leave. She felt that this period was the most upsetting of her whole life, and she was worse than ever before, being unable to swallow and suffering from a flare-up of the arthritis which forced hospitalization at home.

Even after leaving, her mother continued to write insulting letters and made every effort to move back into their home. Her husband wanted to return the letters unopened and to sever relations absolutely, but the patient did not feel that this was right. She said she could never have her mother in her home, but did not know what she could do about the situation otherwise, because she loved her mother in spite of the latter's selfishness and domineering behavior. She recognized the fact that her mother wanted to run everyone's life, "ran mine until I was married," and was now attempting to ruin her marriage. Because of these mixed emotions, she didn't know which way to turn, despite her love for her husband. Before the patient came to the clinic, the intercession of a clergyman with her mother had proved fruitless, and the mother refused to see a psychiatrist.

This was basically the situation at the time the patient was seen. She was quite anxious and tense, and during the first few days of her examination electroshock therapy was considered because of severe depression. However, after a few visits, in which there was considerable ventilation, the depression lifted to a large extent and she felt much better. She realized that she must make a decision regarding her mother, and reiterated the fact that she had always resented never being allowed to make any of her own decisions. Now she felt that she wanted to stand on her own feet.

Follow-up Note. In August, 1947, several months after the foregoing history had been taken, a letter was received from the patient asking that the clinic records be changed back to her maiden name. Evidently she had been unable to make a success of her marriage and had been divorced in the interim. She later left for Arizona for treatment of the arthritis.

Summary. Seldom have we seen a patient with such a domineering parent and so completely dominated. Despite her superior intelligence, she was completely un-

able to establish any degree of emotional independence and maturity. The deep-seated neurosis was further reflected in her frigidity and depression. She was well aware of the relation of psychic trauma to the onset and to each recurrence of her cardiospasm. (One might speculate also on the relation of these same emotional factors to the flare-ups of rheumatoid arthritis.)

COMMENT

An analysis of the complete group of cases revealed that a number of environmental and emotional factors were operative at the time of onset of the patients' somatic symptoms. An attempt was made to group those of like nature under a common heading, although it is recognized that in many cases more than one factor may have contributed to the patient's illness.

1. *Resentment or anger* was the paramount factor in 16 cases. This was exhibited toward a husband, wife, son, daughter-in-law, family as a whole, working conditions, or as the result of an injury. In two other cases, outward humiliations occurred just before the onset of symptoms. In these patients, resentment seemed to be the primary affective expression. In fact, it would be difficult to point out a history in which this did not contribute in at least some degree toward the patient's emotional problems.

2. *Economic loss or insecurity*, such as loss of funds or business, was important in six cases, albeit to varying degree. At times it verged on the catastrophic.

3. In four cases *death of a parent* on whom the patient was abnormally dependent played an important part in the patient's reaction. In another case departure of a brother for military service was undoubtedly equated with death in the mind of the patient.

4. *Feelings of rejection*, such as by a daughter, sister or the entire family group, were prominent in four cases.

5. *Fears* of death, insanity or failure were noted in an additional three cases. These were undoubtedly displacement reactions.

6. *Frustration* seemed to be the paramount factor in one case, although it was seen coincidentally in many other patients.

7. Symptoms were noted to follow the *menopause* in two cases, and physical illness or surgical procedure in three additional cases. In such patients, it should be pointed out, the significance to the value system of the individual concerned cannot be ignored. This has been discussed previously.

It seems worthy of comment that factors of secondary gain were apparent in at least three cases. In other words, the physical disability incident to cardiospasm was a distinct advantage to the patient in many ways as partial solution of the problems and conflicts of the total life situation.

These case histories would seem to bear out Faulkner's contention [21] that cardiospasm is a disease of the frustrated and is not seen in happy, contented and well-adjusted individuals. I believe it reasonable to say that deep-rooted feelings of resentment, frustration and anxiety were the most common emotional reactions encountered in the group studied. That these

emotions were handled in an abnormal or neurotic fashion was apparent from the large number of other neurotic reactions exhibited in these patients aside from their complaint of dysphagia. These reactions have been discussed previously and included depressions, frigidity, abnormal grief, anxiety states and the like. Psychiatrists have long been aware that the main element in a depression is the hostility, anger or resentment which the individual feels toward his environment, yet suppresses. It was interesting to note not only the number of cases in which this specific effect was present, but also the characteristic inability of the patient with cardiospasm to externalize his affective relationships. These factors would be consistent with current psychopathologic concepts and thus account for the number of depressions noted in the present series.

As a group, patients with this condition seemed to have been beset with unusual problems and difficulties, viewed in the light of their value system. As several of them put it, in discussing their tribulations, problems continued to mount up until finally something came along which was more than they could take or "swallow." Such expressions as the foregoing are frequently used by individuals to typify their life situation, and provide an interesting application of the use of so-called organ language in describing the psychopathology.

That the soil was fertile for psychoneurotic reaction patterns is evident not only from the large number of neurotic traits in other members of the family but from the personality disturbance in individual patients which could be traced to childhood.

It should again be pointed out that many of the conflicts and personality factors seen in patients with cardiospasm are by no means unique in this disease but may be seen in many other neurotic individuals. Saul,[38] in his analytic study of seven hypertensive patients and eight controls, discussed the same problem. He did not find hypertension in individuals who, though they have the same conflict as hypertensive patients, have nevertheless workable solutions for their difficulty. He suggested that "the status of the conflict may be peculiar to cases of essential hypertension." The Adlerian concept has been referred to previously. Further information is also necessary to determine whether globus hystericus and diffuse spasm of the esophagus differ psychodynamically from cardiospasm and, if so, in what respects.

In any discussion of the rôle of emotional factors in cardiospasm, as well as psychosomatic problems in general, it is well to exclude the possibility of chance and the noncontributory concatenation of events. These factors can be assayed only in light of the individual's value system. For instance, if a certain event actually or symbolically has great significance to an individual, it is more likely to evoke a reaction than some indifferent stimulus. The patient in case 2, whose symptoms came on the first time he attempted to eat following an injury to his hand, is a good illustration of this point. After so many years of hardships and failure, this episode was considered to be the last straw, the "climax" of his bad luck, as he expressed it.

What is the rôle of the autonomic nervous system in cardiospasm? Knight's [16] original work indicated this system as mediating an end organ effect at the cardia. The value of this work is enhanced not only by the failure to demonstrate a true sphincter in an anatomic sense, but also by the functional, intermittent or varying nature of the symptoms of patients who have cardiospasm. These fluctuations are commonly noted, as was previously pointed out, to be responses to so-called nervous tension factors. Though symptoms seldom completely abate in the absence of treatment, patients often note inability to force any food through the cardia under certain circumstances (for example, eating in a public restaurant) and yet may experience relatively little or no trouble eating a short time later. Unanswered is the effect of autonomic imbalance on other smooth muscle areas in the gastrointestinal tract (pylorus, and so forth) whose innervation is similar to that of the cardia. That disturbances may be present in certain cases may be conjectured from the occasional association of cardiospasm with peptic ulcer.

As Binger and associates [39] have pointed out in regard to hypertension, the problem of pathogenesis is also unanswered, and in the present state of our knowledge suitable methods are still not available "to test the question of causation in the dynamic interrelationship of psyche and soma." It may be that the emotional conflicts of the cardiospastic patient are capable of initiating a flow of impulses over the sympathetic fibers to the cardia, preventing normal vagal relaxation before a bolus of food. This must remain speculative until further evidence is at hand.

In explaining the remaining manifestations of cardiospasm, we would seem to be on much safer ground. The dilatation of the esophagus above the cardia is more than likely due to the stretching which results from efforts to force food into the stomach as well as the piling up of food above the cardia. In the ordinary successful dilatation it would seem that the muscle and connective tissue fibers at the cardia are stretched in such a way as to produce an incompetent sphincter incapable of reacting to nervous or other stimuli. Swallowed food is thus passed without difficulty. Etzel [40] has described a group of cases in which mega-esophagus, megacolon, mega-ureter and other changes were noted and attributed to chronic deficiency of thiamin. Such a "syndrome" is unusual in this country and raises the question whether cardiospasm is a single or multiple entity. Closer examination of our cases might possibly reveal some of the changes described by Etzel. By the same token, further studies of the changes in Auerbach's plexus at the cardia, both in normal persons and in those cases of cardiospasm which come to necropsy, are certainly indicated.

The occurrence of cardiospasm in children, albeit rare, is a further problem for study. One of us (Moersch [41]) reported that, of 691 patients seen at the Mayo Clinic until 1928, 34 dated the onset of symptoms before the age of 14 years and 12 were less than 14 years of age when they came to the clinic. There were three cases in which symptoms began in the first

year of life. The one child in the present series presented numerous emotional problems, and certainly it is becoming increasingly apparent that children are as vulnerable to psychic trauma as adults. No conclusions applicable to children in general can be drawn from a single case, however, and further investigation along these lines by one trained in child psychiatry would be exceedingly helpful. The fact that the disorder has been described in the first few days of life would seem to exclude the psychic factor as being present in all cases.

At this point it may be well to discuss the essential difference between conversion hysteria and vegetative neurosis because of the bearing on the present work. Alexander and French [42] have stated: "A conversion symptom is a symbolic expression of a well-defined emotional content, an attempt at relief. It is expressed by the voluntary neuromuscular or sensory perceptive systems whose original function is to express and relieve emotional tension." (Because it is an attempt or diversion of affect from the real conflict, "la belle indifférence" in the true conversion hysteria is readily understandable.) They continued: "A vegetative neurosis like emotional hypertension is not an attempt to express an emotion, but is the physiological accompaniment of constant or periodically recurring emotional states." Viewed in this light, if the material uncovered in the present study has any significance from the standpoint of pathogenesis, cardiospasm should be classed as a vegetative neurosis, not a conversion hysteria, as suggested by Weiss.[32] That there were concomitant emotional states in these individuals cannot be denied.

Finally, it is important that some discussion be had of the practical application in treatment of the foregoing information regarding emotional problems and personality factors in this disease. This is a problem with many aspects and variables, and the answer is not simple. From the statistical point of view, about 71 per cent of patients obtain permanent symptomatic relief from dilatation of the cardia.[43] I know of no comparable group which has been treated by psychotherapy alone. However, Ripley, Wolf and Wolff,[44] reporting on treatment in a psychosomatic clinic, stated that 19 per cent of their patients were basically improved and 38 per cent were symptomatically improved. (A variety of conditions and therapeutic procedures were included.) However, according to the "psychosomatic" concept postulated, treatment should be holistic, an approach which ignores neither the psyche nor the soma. This immediately raises three questions, which are not completely answered at this time:

1. What happens if the emotional problems of these patients are ignored and treatment is purely "somatic" (that is, by dilatation or other operative procedure)? At present there is little or no information regarding this point, except an indication that those patients who respond poorly to dilatation or whose emotional problems continue unabated are more likely to have recurrences of symptoms than other patients. The more immediate

emotional reaction of the patient whose symptoms are removed by dilatation is worthy of study.

Weiss [32] has pointed out that the physical disorder may be necessary to the emotional life of the patient and that until the psychic conflict is solved, the particular disorder from which the patient suffers must be either maintained or replaced by another illness. He pointed out that one of his patients became depressed immediately following dilatation treatment. Szasz [45] studied a group of Dragstedt's patients who had undergone vagotomy for peptic ulcer and noted that 37 per cent continued to have some type of difficulty, even though their ulcer had completely healed. One patient became a heavy drinker, and a second became definitely worse and remained incapacitated (psychologically) during the period of observation. Adlersberg and Hammerschlag,[46] in a study of the "postgastrectomy syndrome," pointed out that a majority of the patients in their group presented stigmata of psychoneurosis, with tendency to fixation and overemphasis of symptoms. As in the present study, psychoneurotic trends could be traced back to the period preceding gastrectomy and even preceding the onset of the disease. Often some of the "early" postprandial symptoms could be alleviated by psychotherapy. They felt that this syndrome was due to a combination of mechanical and chemical factors with distinct psychoneurotic disturbances. This emphasizes the need to answer the question: What happens to the patient following treatment? as well as What happens to his dysphagia?

2. Is dilatation in itself of value psychotherapeutically? There are certain indications that this not only is true but should be considered by the clinician in handling these patients. For instance, Gill [47] observed that a group of 20 patients, each with a chronic gastric ulcer, whose only treatment consisted of hypodermic administration of 1 c.c. of distilled water while hospitalized, with disregard of rest in bed, medications, diet and prohibition of smoking, were noted with one exception to lose their pain and undergo healing of their ulcers just as quickly as a control group treated along orthodox lines. Gill emphasized that "being in a hospital or getting shots means something to the patient, something which is very important," and pointed out that we should consider the unconscious meaning of the procedure to the patient. Weiss [32] further observed that in one of his female patients with cardiospasm, whose symptoms apparently arose in connection with marital sexual incompatibility, treatment with the dilator at the hands of a woman physician was followed by a poor response but the same treatment at the hands of a man physician resulted in considerable improvement. Attention has likewise been called [48] to the psychologic as well as the physiologic advantages of the Kempner regimen in hypertension, pointing up this aspect in still another condition.

One can merely speculate as to the psychotherapeutic benefits of dilatation in cardiospasm and how these forces operate. The case histories indicate that, as a group, patients with cardiospasm are passive and dependent.

We might speculate that the endoscopist, being in an authoritative position and using an unequivocal approach, helps the patient in some way by supplementing the forces of repression.   On the other hand, perhaps dilatation has the symbolic significance of punishment for unconscious guilt feelings.

3. Should an *additional* psychiatric approach be used in treatment and, if so, when?   There are many variables which influence the answer to this question, some of which are the factors which influence the selection of patients suffering from emotional problems for psychotherapy in general. It is well known that allowing patients to ventilate their problems lightens the emotional burden and is often in itself of great psychotherapeutic benefit. This approach can be followed by the sympathetic clinician and, accompanied by efforts to modify or improve the life situation, may be all that is necessary. (It is assumed that the patient receives adequate dilatations concurrently, for it is just as wrong to ignore the soma as to ignore the psyche.)   Those patients whose symptoms tend to recur, or whose difficulties and personality disturbances are more profound, might benefit from additional psychiatric help, given in close coöperation with the clinician who is handling the problem.

No matter what conclusions the reader draws from the material presented in this paper in regard to the etiology of cardiospasm, it is apparent that certain facts stand out: Patients with cardiospasm are in general passive, dependent individuals with many common personality factors.   In addition, with one exception, they were found to have multiple emotional problems arising from unpleasant life situations, all viewed in the light of the individual's own value system.   Realizing that there are many gaps in our knowledge not only of the interplay between psyche and soma, but of cardiospasm in general, many of which have been pointed out, it is suggested that such emotional factors may attain etiologic significance in certain cases.

Even those who disagree with this statement can have no objection to our general rôle as physicians to help those who are sick or who come to us with their problems, no matter what the basis.   Thus there can be no argument with the aim of the truly psychosomatic approach in cardiospasm, that is, to help these patients not only by improving their swallowing but by lightening their emotional burdens and life problems.   As Burlingame[**] stated: "Although a physician may treat a disease, he certainly cannot treat it with maximum success without treating the individual."

SUMMARY

An inquiry has been made into the pathogenesis of cardiospasm by studying, from the psychiatric point of view, a group of 25 patients suffering from this disorder.   The following findings have been noted.

1. Twenty-four patients suffered from emotional trauma, viewed in the light of the individual's own value system, at the time of onset of symptoms.

This was absent in the twenty-fifth patient, who was so withdrawn and hard to approach that a good rapport could never be established, and yet who presented the personality factors noted in other patients.

2. In general, symptoms tend to be aggravated when the patient is "nervous" or upset, and to be less severe or absent when things are going along smoothly. It was pointed out that such fluctuations in the clinical course, which can occur at times in less than a minute, are a strong argument that cardiospasm is a so-called functional disturbance. Recurrences are noted to follow repeated or new psychic trauma.

3. A number of environmental factors and emotional reactions were noted to be present at the time of onset of symptoms. These included hostility and resentment, economic loss or insecurity, death of a parent on whom the patient was unusually dependent, feelings of rejection, fears of death, insanity or failure, frustration, the menopause and surgical procedures. Factors of secondary gain were noted in three cases.

4. As a group, these patients were noted to be passive, dependent individuals with many common personality features. They gave evidence of personality difficulties in childhood, plus other neurotic manifestations in adult life. Many were depressed. These findings bear out a previous observation that cardiospasm is a disease of the frustrated and is not seen in happy, contented and well-adjusted individuals.

5. Some of the gaps in our present knowledge of cardiospasm have been indicated, and the therapeutic implications of the foregoing findings have been discussed.

BIBLIOGRAPHY

1. Bockus, H. L.: Gastro-enterology. The esophagus and stomach: examination of the patient, and diagnosis and treatment of disorders of the esophagus and stomach, including duodenal ulcer, 1944, W. B. Saunders Company, Philadelphia, vol. 1, p. 91.
2. Editorial: The meaning of psychosomatic medicine, New England J. Med. 236: 83–84, 1947.
3. Menninger, W. C.: Psychosomatic medicine; somatization reactions, Psychosom. Med. 9: 92-97, 1947.
4. Raginsky, B. B.: Psychosomatic medicine. Its history, development and teaching, Am. J. Med. 5: 857–878, 1948.
5. Editors: Introductory statement, Psychosom. Med. 1: 3–5, 1939.
6. Halliday, J. L.: The significance of "the concept of a psychosomatic affection," Psychosom. Med. 7: 240–245, 1945.
7. Willis, T.: Cardiospasm. In Major, R. H.: Classic descriptions of disease with biographical sketches of the authors, Ed. 2, 1939, Charles C Thomas, Springfield, Illinois, p. 687.
8. Sturtevant, M.: Cardiospasm, with a review of the literature, Arch. Int. Med. 51: 714-736, 1933.
9. Zenker, F. A., and von Ziemssen, H. W.: Krankheiten des Oesophagus, Handbuch der speciellen Pathologie und Therapie, 1874, F. C. W. Vogel, Liepzig, vol. vii, pp. 1-208.
10. Plummer, H. S.: Cardiospasm, with a report of forty cases, J. A. M. A. 51: 549-554, 1908.

11. Plummer, H. S.: Diffuse dilatation of the esophagus without anatomic stenosis (cardiospasm). A report of 91 cases. Collect. Papers Mayo Clin. and Mayo Found. 6: 3–7, 1912.

12. Moersch, H. J.: Cardiospasm: its diagnosis and treatment, Ann. Surg. **98**: 232–238, 1933.

13. Rake, G. W.: On the pathology of achalasia of the cardia, Guy's Hosp. Rep. **77**: 141–150, 1927.

14. Lendrum, F. C.: Anatomic features of the cardiac orifice of the stomach with special reference to cardiospasm, Arch. Int. Med. **59**: 474–511, 1937.

15. Vinson, P. P.: Cardiospasm, Am. J. Surg. **56**: 79–86, 1942.

16. Knight, G. C.: The relation of the extrinsic nerves to the functional activity of the oesophagus, Brit. J. Surg. **22**: 155–168, 1934.

17. Knight, G. C., and Adamson, W. A. D.: Achalasia of the cardia, Proc. Roy. Soc. Med. **28** (pt. 2): 891–897, 1935.

18. Mitchell, G. A. G.: The nerve-supply of the gastro-oesophageal junction, Brit. J. Surg. **26**: 333–345, 1938.

19. Plummer, H. S., and Vinson, P. P.: Cardiospasm: a report of 301 cases, M. Clin. North America **5**: 355–369, 1921.

20. Winkelstein, A.: Psychogenic factors in cardiospasm, Am. J. Surg. **12**: 135–137, 1931.

21. Faulkner, W. B., Jr.: Cardiospasm; report of a case and discussion of improper treatment, West. J. Surg. **48**: 561–563, 1940.

22. Faulkner, W. B., Jr.: Objective esophageal changes due to psychic factors. An esophagoscopic study with report of 13 cases, Am. J. M. Sc. **200**: 796–803, 1940.

23. Faulkner, W. B., Jr., Rodenbaugh, F. H., and O'Neill, J. R.: Influence of the emotions upon esophageal function: a comparison of esophagoscopic and roentgenologic findings, Radiology **37**: 443–447, 1941.

24. Faulkner, W. B., Jr.: Esophageal spasm. Observation of emotional influences by means of the esophagoscope: report of a case, J. Nerv. and Ment. Dis. **93**: 713–715, 1941.

25. Mitchell, H. E.: Achalasia of esophagus, with report of case relieved by esophagogastrostomy, Ann. Otol., Rhin. and Laryng. **50**: 662–674, 1941.

26. Emery, E. S., Jr.: Cardiospasm, Rev. Gastroenterol. **9**: 112–115, 1942.

27. Dunbar, H. F.: Emotions and bodily changes; a survey of literature on psychosomatic interrelationships, Ed. 3, 1946, Columbia University Press, New York, 291–293.

28. Marcondes, D.: Sôbre a psicogénese do "mal engasgo," Arq. neuro-psiquiat., São Paulo **5**: 125–133, 1947.

29. Bockus, H. L.: Gastro-enterology. The esophagus and stomach: examination of the patient, and diagnosis and treatment of disorders of the esophagus and stomach, including duodenal ulcer, 1944, W. B. Saunders Company, Philadelphia, vol. 1, p. 97.

30. Romano, J.: Personal communication to the authors.

31. Walsh, M. N.: Personal communication to the authors.

32. Weiss, E.: Cardiospasm: a psychosomatic disorder, Psychosom. Med. **6**: 58–70, 1944.

33. Conn, J. H.: Psychogenic factors in diseases of digestion, Gastroenterology **9**: 399–408, 1947.

34. Braceland, F. J., and Giffin, M. E.: The mental changes associated with multiple sclerosis (an interim report), A. Research Nerv. and Ment. Dis. Proc. **28**: 450–455, 1950.

35. Binger, C. A. L., Ackerman, N. W., Cohn, A. E., Schroeder, H. A., and Steele, J. M.: Personality in arterial hypertension, 1945, The American Society for Research in Psychosomatic Problems, New York, p. 3.

36. Smith, G.: Psychotherapy in general medicine; report of an experimental postgraduate course, 1946, The Commonwealth Fund, New York, 38 pp.

37. Rennie, T. A., and Bauer, W.: General orientation. *In* Witmer, H. L.: Teaching psychotherapeutic medicine; an experimental course for general physicians, 1947, The Commonwealth Fund, New York, pp. 58–62.

38. Saul, L. J.: Hostility in cases of essential hypertension, Psychosom. Med. **1**: 153–161, 1939.

39. Binger, C. A. L., Ackerman, N. W., Cohn, A. E., Schroeder, H. A., and Steele, J. M.: Personality in arterial hypertension, 1945, The American Society for Research in Psychosomatic Problems, New York, p. 225.

40. Etzel, E.: May the disease complex that includes mega-esophagus (cardiospasm), mega-colon and mega-ureter be caused by chronic vitamin B_1 deficiency? Am. J. M. Sc. **203**: 87–100, 1942.

41. Moersch, H. J.: Cardiospasm in infancy and in childhood, Am. J. Dis. Child. **38**: 294–298, 1929.

42. Alexander, F., and French, T. M.: Studies in psychosomatic medicine; an approach to the cause and treatment of vegetative disturbances, 1948, Ronald Press Co., New York, p. 7.

43. Moersch, H. J.: Personal communication to the authors.

44. Ripley, H. S., Wolf, S., and Wolff, H. G.: Treatment in a psychosomatic clinic, J. A. M. A. **138**: 949–951, 1948.

45. Szasz, T. S.: Psychiatric aspects of vagotomy: a preliminary report, Ann. Int. Med. **28**: 279–288, 1948.

46. Adlersberg, D., and Hammerschlag, E.: Mechanism of the postgastrectomy syndrome, J. A. M. A. **139**: 429–437, 1949.

47. Gill, A. M.: Pain and the healing of peptic ulcers, Lancet **1**: 291, 1947.

48. Editorial: The therapeutic rôle of the Kempner diet, New England J. Med. **240**: 236, 1949.

49. Burlingame, C. C.: What the physician can expect from psychiatry, M. Ann. District of Columbia **17**: 655–660; 701, 1948.

THE CORRELATION BETWEEN THE Q WAVES OF aVF AND ESOPHAGEAL LEADS IN THE DIAGNOSIS OF POSTERIOR MYOCARDIAL INFARCTION *

By Ira L. Rubin, M.D., and O. Alan Rose, M.D., *New York, N. Y.*

The significance of a deep Q wave in standard Lead III as an aid to the diagnosis of posterior myocardial infarction was established by Pardee[1] in 1930. Since this time a deep Q_3 has been of accepted value in this diagnosis. It has been recognized, however, that a significant Q wave in standard Lead III according to Pardee's criteria (25 per cent or more of the highest R wave in the standard leads) may be seen in normal patients. It is also known that a Q wave of apparently significant amplitude may be present in conditions other than myocardial infarction. On the other hand, Q_3 may be small or absent in posterior wall myocardial infarction.

More recently, two other electrocardiographic leads have been found to show more consistent Q wave correlation in the evaluation of posterior myocardial infarction. These are the esophageal leads at ventricular levels and the unipolar lead from the left lower extremity. The esophageal leads were developed by Lieberson and Liberson[2] and by Brown.[3] They have been evaluated clinically by Hamilton and Nyboer[4] and others. The unipolar extremity leads were introduced by Wilson and his group.[5] They have been "augmented" with further evaluation and have been termed the aV leads by Goldberger.[6]

The correlation of Q waves in aVF and in the esophageal leads at ventricular levels in posterior myocardial infarction has been shown to be excellent. Myers and Oren,[7] using the esophageal leads as a criterion of posterior myocardial infarction, found excellent agreement between Q waves in esophageal leads at ventricular levels and significant Q waves in Lead aVF. Nyboer[8] also found similar agreement between the aVF and the esophageal leads. In the evaluation of posterior myocardial infarction, lead aVF is commonly used in preference to the esophageal leads because of technical simplicity.

The following is part of a study of 75 patients whose electrocardiograms showed Q waves in standard Lead III. Unipolar extremity potentials and esophageal leads were taken on each patient. There was excellent correlation in most of these cases between the presence or absence of Q waves in both the esophageal leads at ventricular levels and aVF with the clinical and

postmortem findings of posterior myocardial infarction. In eight cases this correlation was not complete. An analysis of these cases is the subject of this report.

Two patients with posterior myocardial infarction had deep Q waves in their esophageal leads at ventricular levels but no significant Q waves were present in Lead aVF. These cases are presented.

CASE REPORTS

Case 1. The first patient was a 46 year old white male who had had pernicious anemia for 10 years. He had several relapses due to his failure to take liver injections. On August 30, 1947, he had an episode of pain typical of myocardial infarction. His clinical course and laboratory findings were consistent with this diagnosis. The esophageal study was performed seven weeks after the onset of pain.

This patient had had a normal electrocardiogram in 1941 (figure 1). Despite the serial changes in the T waves in Leads II and III, no significant Q waves appeared in Lead III or aVF at the time of the electrocardiographic study in 1947. The diagnosis of posterior myocardial infarction is supported by the Q and T wave abnormalities which are seen in the esophageal leads at ventricular levels. The T wave changes in Leads II, III and aVF are also consistent with this diagnosis. However, the Q wave in aVF in this case cannot be considered to be a significant one and does not correlate with the above findings.

Case 2. The second patient was a 57 year old white male who was admitted with a history of having experienced two attacks of precordial pain in the previous six years. Five weeks and again two weeks prior to admission, he had had precordial pain lasting several hours. After admission he continued to have attacks of precordial pain at rest. There was no fever or leukocytosis. The erythrocyte sedimentation rate was 16 mm./hr. (Wintrobe method).

The electrocardiograms in this case (figure 2) show T wave changes in Lead I and in Leads CF_3 and CF_5 which are consistent with the diagnosis of anterior myocardial infarction. It cannot be definitely determined from the standard leads that posterior myocardial damage has also occurred. In aVF the Q wave is of short duration and of low amplitude, and it is not considered to be significant. In the esophageal lead with the electrode 65 cm. from the nares there is a QS complex followed by a low inverted T wave. Q waves at higher ventricular levels are not of significant amplitude, but T waves are inverted at all ventricular levels and are upright at auricular levels. These Q and T wave findings in the esophageal leads are evidence of posterior myocardial infarction. It appears that there has been both anterior and diaphragmatic myocardial infarction in this case. Lead aVF does not correlate with the significant changes in the esophageal leads.

Four patients with posterior myocardial infarction had deep Q waves in Lead aVF but deep Q waves were not present in the esophageal leads at ventricular levels. Two of these cases are presented.

Case 3. The first patient was a 51 year old white male who had had an episode of chest pain typical of myocardial infarction 36 hours prior to admission. His clinical course and laboratory findings were consistent with this diagnosis. The first electrocardiogram was taken on admission, October 21, 1947. The remaining tracings were taken one month later (figure 3).

IRA L. RUBIN AND O. ALAN ROSE
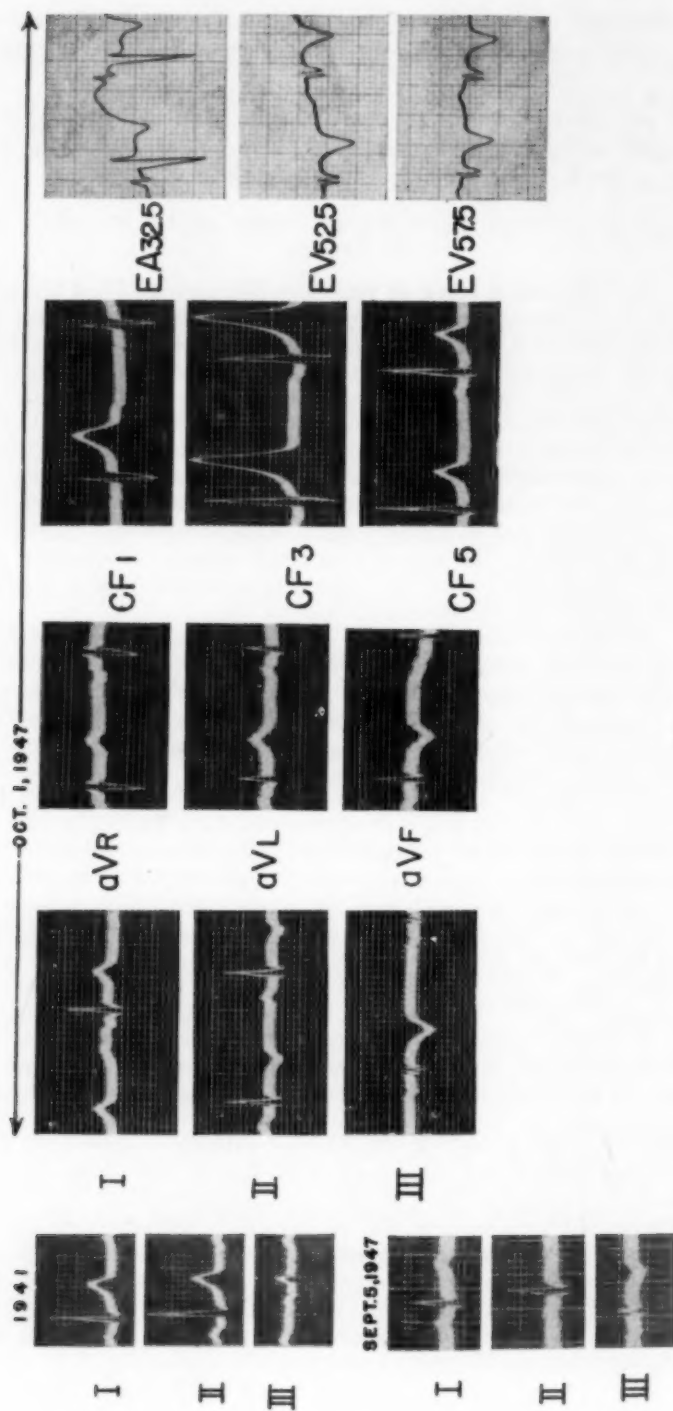
FIG. 1.
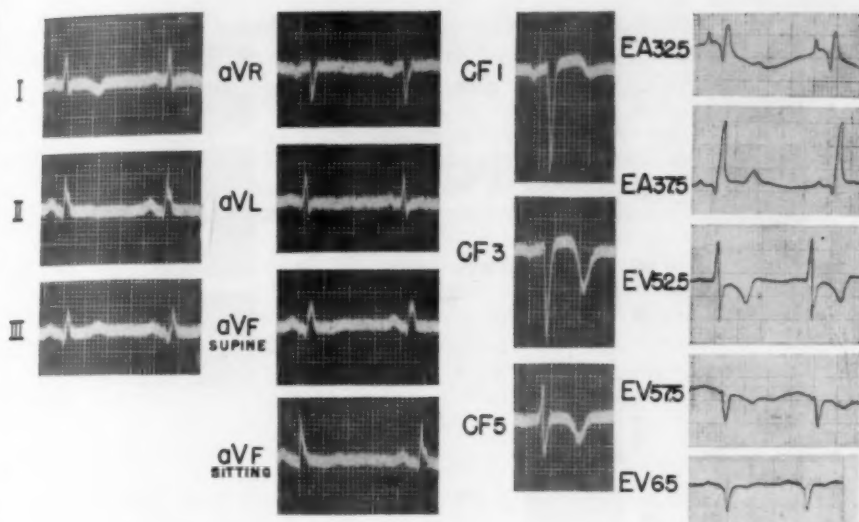
FIG. 2.

There is a deep Q wave in standard Leads II and III, with serial S–T and T wave changes and a deep Q in aVF which indicate the presence of posterior myocardial infarction.   However, the esophageal leads at ventricular levels show Q waves which are not significant according to existing criteria.[8]

Case 4.   The second patient was a 57 year old white male who had had known diabetes and hypertension since 1941.   In 1945 he was hospitalized because of severe precordial pain.   His clinical course and laboratory findings were compatible with the diagnosis of myocardial infarction.   Since that time he had had angina on exertion which was relieved by nitroglycerin.   The patient was admitted for treatment of diabetes and peripheral vascular disease.

This patient had had a relatively normal electrocardiogram in 1941, except for the pattern which is consistent with left ventricular hypertrophy (figure 4).   Serial electrocardiograms in 1945 show deep Q waves in Leads II and III, with associated
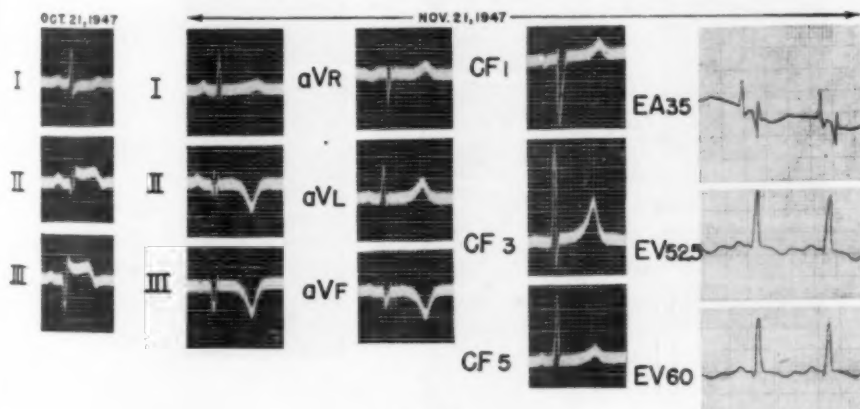
FIG. 3.
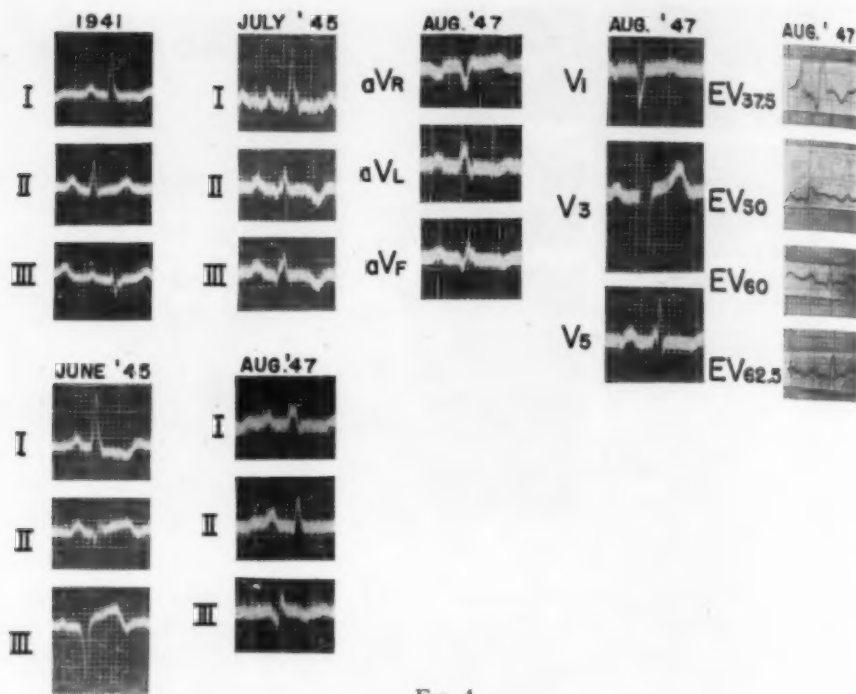
FIG. 4.

S–T and T wave changes which are consistent with the diagnosis of posterior myo-
cardial infarction. At the time of our study, two years later, in August of 1947,
there is a deep Q wave in standard Lead III and in Lead aVF. Esophageal leads at
ventricular levels show Q waves which are not significant according to existing
criteria.[8]

FIG. 5.

Two patients who had no evidence of organic heart disease had deep Q waves in Lead aVF without corresponding deep Q waves in their esophageal leads. One of these cases is presented.

Case 5. The patient was a 21 year old colored male who was hospitalized for acute infectious hepatitis. The liver was enlarged 3 cm. below the costal margin. At no time did he complain of precordial pain or symptoms of diminished cardiac reserve. There was no history or clinical evidence of syphilis, rheumatic fever or hypertension.

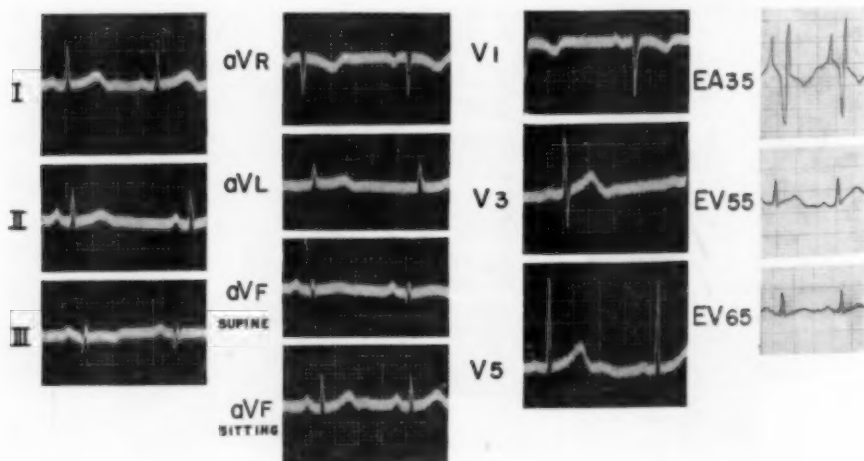In the electrocardiograms of this patient (figure 5) there is a deep Q wave in Lead III which is followed by a diphasic T wave. In aVF in the supine position there is a Q wave which is equal in amplitude to the R wave. In the sitting position this Q wave almost entirely disappears. Esophageal studies are normal. In this case, with the patient in the supine position a significant Q wave is seen in aVF. There are no corroborative Q wave findings in the esophageal leads.

DISCUSSION

It is not surprising that correlation in the Q waves in standard Lead III, Lead aVF and the esophageal leads at ventricular levels is not complete. This lack of correlation is due largely to the difference in the derivation of these three leads.

Standard Lead III is the least reliable of the three methods in evaluating posterior myocardial infarction because of its bipolar derivation. Potential variations in the left upper extremity lead (as seen in aVL) reciprocally combine with potential variations in the left lower extremity lead (as seen in aVF), to produce the conjugation of the complexes in standard Lead III. For this reason an early positive deflection in aVL can produce a Q wave which may be of significant amplitude in standard Lead III. This is frequently seen as the so-called "physiological Q" wave when a normal heart is transversely rotated in the thorax on its anterior-posterior axis. Conversely, rotational factors or anterior myocardial infarction may produce an initial negative deflection in aVL. This negative deflection may neutralize or obliterate a significant Q wave in aVF and result in an absent or insignificant Q_3. Analysis of aVL and aVF will frequently clarify unexplained Q wave findings in standard Lead III.

The esophageal leads and aVF have been found to correlate with considerably greater accuracy than standard Lead III in evaluating the diagnosis of posterior myocardial infarction. The esophageal lead and Lead aVF are unipolar in type. It is believed that when unipolar leads are so placed as to reflect the electrical activity from an infarcted area of myocardium, an initial negative QRS deflection is produced because under this circumstance these leads act as "semidirect" leads from the cavity of the ventricle. It is known that the esophageal lead and Lead aVF reflect the electrical activity from the posterior or diaphragmatic surface of the heart. A deep Q wave in the esophageal leads taken at ventricular levels and in aVF is therefore theoretically a significant finding as evidence of posterior myocardial infarction.

However, there are occasional sources of error in both aVF and the eso-
phageal leads in evaluating the condition of the posterior myocardium.

A possible source of error in aVF is that the left leg electrode is at a
considerable distance from the heart.   Damage of the posterior myocardium
may not be reflected to the left leg electrode.   Nyboer [8] stated that it is
possible that an area of myocardial infarction which is high in the posterior
wall of the left ventricle may not be reflected to the left leg electrode and
may only be evident in esophageal leads at high ventricular levels.   Patients
1 and 2 (figures 1 and 2) appear to have posterior myocardial damage as
indicated by the esophageal leads.   Both had clinical evidence of myocardial
infarction with serial electrocardiographic findings consistent with involve-
ment of the posterior wall, but the Q waves in aVF are not significant in
either case.   In view of Nyboer's concept, it is of interest that on eso-
phageal electrocardiographic examination the area of infarction was ap-
parently not localized high on the posterior wall in either patient.   In case
2 (figure 2), abnormal Q waves are found only at the lowest ventricular
level in the esophageal leads.   At this level the electrode was probably in
the stomach, and thus it may reflect a localized area of diaphragmatic myo-
cardial infarction.   The infarcted area may have been poorly oriented with
respect to this patient's left leg electrode.   This could account for the ab-
sence of a significant Q wave in the aVF lead in this case.

A possible source of error in esophageal electrocardiography is that
the esophageal electrode explores only a small portion of the posterior and
diaphragmatic surfaces of the heart.   The esophageal electrode may be
compared to a precordial electrode which is moved in a vertical direction on
the chest wall.   Well localized infarcted areas of the posterior myocardium
may be located to one or the other side of the esophagus.   In this circum-
stance the esophageal electrode might not reflect the electrical activity of
the injured area, whereas the more distant left leg electrode might be better
oriented with respect to the infarct.   This may well be the explanation of
the most common failure of correlation in our series: the finding of a deep
Q in aVF with normal esophageal leads.   This lack of correlation was found
in four of our patients.   All four of these patients had good clinical and/or
serial electrocardiographic evidence of posterior myocardial infarction.

It is theoretically possible that a small, well-localized infarct of the
posterior or diaphragmatic surface of the heart might not be reflected to
either the esophageal or the left leg electrodes.   This could occur if an in-
farcted area were so situated as to be too high on the posterior surface of
the heart to be reflected to the left leg electrode and too far lateral to the
esophagus to produce changes in the esophageal leads.   An infarct in this
location might not be identifiable by the use of any of the present electro-
cardiographic leads.

Significant Q waves are occasionally seen in Lead aVF in individuals
with no clinical evidence of myocardial damage.   In case 5 (figure 5), the
patient had no evidence of clinical heart disease, and the esophageal leads

were normal. However, when an electrocardiogram was taken with the patient in the supine position, a significant Q wave was present in aVF. In the sitting position, the Q wave almost entirely disappeared. We have studied the effects of position and respiration on the Q waves in aVF and have noted marked variations in the amplitude of the Q wave with positional and respiratory changes. This study will be reported. On the basis of these observations and those of Myers and Klein,[9] we believe that the Q wave which is seen in patient 5 in the supine position may represent reflection of electrical activity of the posterior basal surface of the heart to the left leg electrode. In our series, there were two cases with abnormal Q waves in aVF in individuals with apparently normal hearts. These Q waves greatly diminished in amplitude in both cases when the patients assumed the sitting position. It is interesting that both these cases had enlarged livers. The hepatomegaly may have produced an unusual degree of anterior displacement of the heart on its transverse axis in the supine position to produce a reflection of posterior basalar electrical activity in Lead aVF.

The failure of correlation of the Q waves of aVF and the esophageal leads occurred in eight cases out of our series of 75. This represents a lack of correlation in over 10 per cent, a significant percentage. The best evidence of posterior or diaphragmatic infarction, according to our findings, is the presence of a deep Q wave in esophageal leads at ventricular levels. However, the absence of such a Q wave in esophageal leads at ventricular levels does not rule out posterior myocardial infarction. The presence or absence of a significant Q wave in aVF is usually of diagnostic value. Exceptions in this lead are more frequent according to our results than is currently indicated in the literature. In the analysis of an equivocal tracing, the clinical history, serial electrocardiograms and other abnormal electrocardiographic changes, including those of the T wave and S–T segment, should all be used. There are cases in which no definite electrocardiographic diagnosis can be made even using all the present electrocardiographic methods.

SUMMARY

1. Seventy-five patients with a Q wave in standard Lead III were studied with augmented unipolar extremity potentials of the left leg (aVF) and esophageal leads.

2. In more than 10 per cent of these patients there was no complete correlation between these leads and the diagnosis of posterior myocardial infarction.

3. An analysis of these cases and a discussion of the possible causes for the failure of correlation are presented.

BIBLIOGRAPHY

1. Pardee, H. E. B.: Significance of electrocardiogram with large Q in Lead III, Arch. Int.
   Med. **46**: 470, 1930.
2. Lieberson, A., and Liberson, F.: An internal electrocardiographic lead, Proc. Soc. Exper.
   Biol. and Med. **31**: 441, 1934.
3. Brown, W. H.: A study of the esophageal lead in clinical electrocardiography, Am.
   Heart J. **12**: 1 and 307, 1936.
4. Hamilton, J. G. M., and Nyboer, J.: The ventricular deflections in myocardial infarction
   —an electrocardiographic study using esophageal and precordial leads, Am. Heart J.
   15: 414-424, 1938.
5. Wilson, F. N., and Johnston, F. D.: Electrocardiograms that represent the potential
   variations of a single electrode, Am. Heart J. **9**: 447, 1934.
6. Goldberger, E.: A simple electrocardiographic indifferent electrode of zero potential and
   a method of obtaining augmented unipolar extremity leads, Am. Heart J. **23**: 483,
   1942.
7. Myers, G. B., and Oren, B. G.: The use of the augmented unipolar left leg lead, in the
   differentiation of the normal from abnormal Q wave in standard Lead III, Am. Heart
   J. **29**: 708, 1945.
8. Nyboer, J. C.: Exploratory electrocardiograms extremity, precordial, esophageal and
   discussion of the Q₃. Electrocardiogram, Read at the Fifty-fifth Annual Meeting of
   the Association of Life Insurance Medical Directors of America, October 24-25, 1946.
9. Myers, G. B., and Klein, H. A.: The relation of unipolar limb leads to precordial and
   esophageal leads, Am. Heart J. **35**: 727, 1948.

THE EFFECT OF A SINGLE INSPIRATION IN LEAD III AND A PRECORDIAL LEAD OF THE HUMAN ELECTROCARDIOGRAM *

By GEORGE L. NORRIS, M.D., *Winfield, Kansas,* and EDWARD MASSIE, M.D., F.A.C.P., *St. Louis, Missouri*

INTRODUCTION

THAT respiration changes the contour of the electrocardiogram has been known since Einthoven, Rotherberger, and Winterberg [1] studied the shifting electrical axis of the heart and found that sympathetic stimulation or vagal paralysis produced changes similar to those at first thought due solely to the mechanical effects of movement of the diaphragm. Wilson [2,3] in 1915 reported three cases in which respiration was associated with auriculoventricular dissociation, and one instance in which a partially inverted T_3 became upright and exaggerated. The same changes were brought about by pressure over the right vagus, and were eliminated by atropine. He emphasized that vagal stimulation displaces the pacemaker downward in the sinus node.

Cohn and Raisbeck [4] in 1922, in a study on the relation of the position of the heart to the electrocardiogram, showed that small anatomic axes were associated with deep S_3 deflections and large anatomic axes with deep S_1 waves. In 1925 Resnik and Lathrop [5] reported changes in the cardiac mechanism of a 43 year old patient with Cheyne-Stokes respiration in which the electrocardiogram showed downward displacement of the pacemaker to the auriculoventricular node, depression of auriculoventricular conduction, and slowing of impulse formation at the sinoauricular node. The changes occurred at the end of the period of apnea and at the beginning of the phase of hyperpnea. Digitalis increased and atropine abolished these changes.

Meek and Wilson [6] in 1925 found that displacement of the heart to the right or left with counter-rotation around the longitudinal axis yielded electrocardiograms similar to those of right or left ventricular preponderance; simple rotation to right or left around the anterior-posterior axis gave corresponding curves of preponderance. Doxiades [7] in 1926 obtained tracings on 10 normal infants immediately after birth and before respiration had started. According to this report, the R waves were inverted and the P and T waves were absent during the initial apnea, but with the onset of respiration a rapidly increasing R wave and T wave appeared. In contrast, Easby [15] in 1934 published an electrocardiogram taken on a four and a half

month fetus which showed well defined P–R and T waves in Lead II during the 45 minutes the fetus was viable.

In 1929 Taylor,[16] reporting on electrocardiographic findings in 61 cases of induced pneumothorax, concluded that marked displacement of the heart occurs rarely without axis deviation as manifested by the electrocardiogram. Of his cases, three were classified as examples of complete displacement of the heart to the right.   Two of these patients had electrocardiograms which were quite normal, and the third had only a low voltage R_1 with smaller S_1 to indicate right axis shift.   In the same year, Otto [17] demonstrated that suddenly increasing the intracardiac pressure in the left or right ventricle by clamping the thoracic aorta or pulmonary artery, respectively, caused marked changes in the T deflections.   These changes gradually reverted to preconstriction contour, even though the clamps were kept in place.   Otto suggested the slight shift of the interventricular septum secondary to the pressure changes as a mechanical cause for T wave changes.

Woodruff,[18] in 1933, reporting on 2,000 records, found 74 instances of changes in form with respiration.   In 20 of these 74 cases, fluoroscopy revealed abnormal limitation of the diaphragm in cases in which there were marked electrocardiographic changes with respiration.   Atropine or vagal stimulation did not change the respiratory variations in his cases.   He believed that respiratory effects on the electrocardiogram were more marked in diseased hearts than in normal hearts.

Katz, Gutman and Ocko [8] in 1936 demonstrated the shunting effect produced by contact of the heart with the anterior or posterior chest wall or the diaphragm, and concluded in part that "certain regions of the heart may gain a decided advantage over the rest of the heart in affecting the electrical field merely because they are in contact with a good conductor."   In the same year, Edeiken, Wolferth and Wood [9] studied the significance of upright or diphasic T waves in Lead IV with no other definite electrocardiographic abnormalities.   They mentioned the "notorious" instability of the T wave and stated that it is affected by digitalis, thyroid disease, intoxication and exercise in individuals without evidence of heart disease.   They did not mention any respiratory effect on the contour of T_4.

In a study of normal variations in chest leads, Sorsky and Wood [10] in 1937 concluded that they would consider as an abnormal QRS complex only an absolutely monophasic deflection.   This did not occur once in their series of 150 normal subjects ranging in age from five to 70 years. Master,[11] in 1939, in his study of the roentgen-ray configuration of the heart and the electrocardiogram, showed that inspiration tended to be associated with a right axis shift and that expiration would occasionally result in a shift of the electrical axis to the left.   He also demonstrated that expiration may cause inversion of T_4, while inspiration may bring about the disappearance of the initial upward deflection of the QRS_4.   Hernandez [12] in 1943 studied the electrocardiographic "accidents" in Lead III during

inspiration and concluded that an inverted P_3 which does not become positive with inspiration is abnormal, and that every Q_3 which is not modified by inspiration or which decreases less than 50 per cent of its height by inspiration should be considered abnormal, as should every inverted T_3 which increases in depth on inspiration.

Mazer and Reisinger [13] in 1943 reported a study of 102 cases of "deep Q_3" electrocardiograms and set up criteria for evaluation of such graphs. They quoted Videla as having found a greater decrease in Q_3 with inspiration in individuals without organic heart disease.   The following year Lyle [14] partially refuted Pardee's criteria for the "deep Q_3" and applied Wilson's unipolar extremity leads to a study in which he concluded that the disappearance of Q_3 on inspiration probably is proof that it is a positional phenomenon, that a significant Q_3 may be less than 25 per cent of the QRS amplitude, and that "a small initial upward deflection takes Q_3 out of the coronary class."

METHOD OF STUDY

The purpose of the present study was to determine the frequency and types of respiratory changes in Leads III and CF IV and, if possible, to correlate these changes with the presence or absence of heart disease.   Many interesting and possibly significant questions arose during the study of these electrocardiograms, but we have adhered to the initial objectives in this report.

In this Heart Station it has been a routine procedure to take electrocardiograms with the patient in the supine position and to have the subject take a single deep breath during the recording of the third lead.   For this study the patient was also asked to take a deep breath during the fourth lead. The electrode was held firmly in place, and good contact with the chest wall was assured by rubbing the area briskly with the electrode and electrode jelly. The subjects included patients in Barnes Hospital and out-patients of the Washington University Clinics.   Twenty-three hundred and seven consecutive tracings were obtained and were studied for the effects of a single deep breath in Lead III and in Lead CF IV.   The only records discarded (55) were those in which the patient was too ill to coöperate or in which Lead CF IV could not be obtained.   In Lead III, data were obtained on the auricular and ventricular complexes, but in Lead CF IV only the ventricular complexes were studied because respiratory movement caused considerable distortion of the P wave.

RESULTS

Table 1 shows the type and frequency of changes seen in Lead III and Lead CF IV during a single deep breath in the 575 of this series of records which were reported as "within normal limits."   In Lead III the P waves became more positive in 168 instances (29 per cent), including 20 cases in which an inverted P_3 became upright.   A negative effect on P_3 occurred in

TABLE I

Type and Frequency of Respiratory Changes in 575 Electrocardiograms
Reported as Within Normal Limits

Changes with Respiration	Lead III		Lead CF IV	
	Frequency	Per Cent	Frequency	Per Cent
VOLTAGE Increase	285	49.6	105	18.3
Decrease	109	19.0	205	35.6
Q WAVE AMP. Increase	4	—	2	—
Decrease	43	7.5	2	—
Disappear	74	12.9	8	1.6
Appear	1	—	6	1.0
R WAVE AMP. Increase	353	61.4	71	12.3
Decrease	25	4.3	195	33.9
Disappear	—	—	1	—
Appear	20	3.5	6	1.0
S WAVE AMP. Increase	14	2.4	97	16.9
Decrease	60	10.4	42	7.3
Disappear	16	2.8	5	—
Appear	3	—	2	—
T WAVE AMP. Increase	110	19.1	50	8.7
Decrease	24	4.2	61	10.6
Incr. Positivity	196	34.1	54	9.4
Incr. Negativity	35	6.1	65	11.3
P WAVE AMP. Increase	110	19.1	P Wave not studied in Lead	
Decrease	17	3.0	CF IV because of distortion	
Incr. Positivity	168	29.2	by respiration.	
Incr. Negativity	38	6.6		

38 cases (6.5 per cent), of which 11 became inverted. In contrast to these changes in contour, the P–R interval decreased in nine and increased in seven instances. The QRS and T wave changes with respiration were usually an increase in positivity of the deflections. The amplitude of Q_3 decreased in 43 cases (7.5 per cent), and the Q wave disappeared with inspiration in 74 cases (12.9 per cent). The amplitude of R_3 increased in 353 records (61.4 per cent) and decreased in 25 cases (4.3 per cent), with a total of 378 cases, or 65.7 per cent, showing R wave changes. In tracings which had slurring or notching of Q, R or S waves, there was a tendency for both slurring and notching to decrease if the amplitude increased with inspiration, and to increase if inspiration caused a decrease in amplitude. The S wave decreased in amplitude in 60 records (10.4 per cent) and disappeared in 16 cases (2.8 per cent). T_3 showed increased positivity in 196 instances (34.1 per cent) and increased negativity in 35 cases (6.1 per cent). In no case did an upright T_3 become inverted, but in 29 records (5.0 per cent) an inverted T_3 became definitely upright.

Lead CF IV, in contrast to Lead III, presented respiratory changes with inspiration which indicated a predominating tendency to increase in negativity of the deflections. The R wave decreased in 195 cases (33.9 per cent) and increased in amplitude in 71 cases (12.3 per cent). The S wave decreased in 42 cases (7.3 per cent) and increased in 97 cases (16.9 per

cent). The T wave in this lead became more positive in 54 cases (9.4 per cent), of which four were changed from diphasic to upright by inspiration. In no case did an upright T wave become inverted nor an inverted T wave become upright. The Q wave changes with inspiration were few in number and were almost equally divided between increase in positivity and increase in negativity. In six cases, inspiration caused the appearance of a QS deflection as the result of "disappearance" of the R wave, while the S wave persisted (figure 1). In most cases a respiratory change in Lead III was associated with respiratory changes in Lead CF IV. However, a few cases showed changes in one lead with no changes in the companion lead.

The most common effect of inspiration on the electrocardiogram was a change in rate which occurred in 415 records (72.1 per cent). Table 2 presents the arrhythmias which appeared with deep inspiration. Sinus arrhythmia was graded as slight if the change in rate per minute was less than six beats; as moderate if the change was between six and 10 beats, and as marked if the rate changed by more than 10 beats per minute. On this basis, 269 cases (46.8 per cent) showed slight and 116 cases (20.2 per cent) showed moderate sinus arrhythmia with inspiration. Only three cases showed a marked sinus arrhythmia. Other changes in rhythm with respiration were infrequent and consisted of a single auricular premature contraction in six cases, a single ventricular premature contraction in three cases, and a sinus pause in one case.

Table 3 presents the type and frequency of respiratory changes in the electrocardiograms of patients with heart disease. In an attempt to evaluate the effect of digitalis on respiratory changes, the data were divided into two primary groups, namely, patients receiving digitalis (297) and patients not receiving digitalis (1,435). Further division of each group was made on the basis of axis deviation and, where possible, on the basis of acute or recent myocardial damage, in contrast to long-standing, apparently non-progressive myocardial damage.

TABLE II

Arrhythmias Appearing with Respiration in Leads III and CF IV

| Group | Normal | Digitalis | | | No Digitalis | | | | | Sinus Tachy. | Sinus Brady. |
		L.A.D.	T.P.H.	Norm. Axis	L.A.D.	T.P.H. and Myo. Dam.	L.A.D. and Myo. Dam.	Norm. Axis and Myo. Dam.	Acute Infarct.		
Number of Cases	575	116	33	131	237	145	344	548	76	167	143
Sinus Arrhythmia											
Slight	46.8%	31.9%	27.3%	20.6%	43.0%	70.4%	28.8%	37.8%	35.5%	18.6%	58.0%
Moderate	20.2	6.9	6.1	6.1	17.7	16.6	9.9	13.5	13.2	10.2	18.2
Marked	—	1.7	—	—	1.3	1.4	1.2	1.3	3.9	3.0	1.4
Premature Beats (Auric., Ventric., Nodal)	1.7	6.0	18.1	8.4	3.4	4.9	6.1	4.1	3.9	6.4	2.4
Sinus Pause	—	—	—	—	—	—	—	—	—	1.2	—
A-V Block (2° and 3°)	—	1.7	—	3.1	—	—	—	—	—	—	—
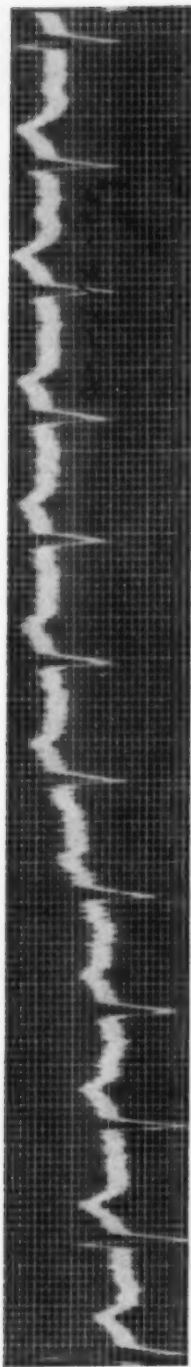
FIG. 1. Case 1475, 40 years, sthenic build, optic neuritis, no digitalis. Lead CF IV. Record demonstrates the change from a normal QRS complex to an abnormal QS complex. There is slight decrease in amplitude of the T waves. The rate decreases during the last four beats.
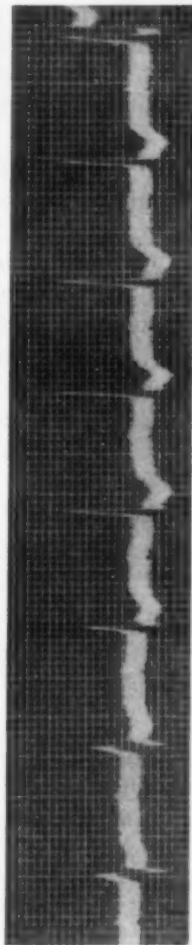
FIG. 2. Case 1993, 50 years, sthenic, rheumatic heart disease, digitalis. Lead III. In this record, in addition to progressive increase in amplitude of the R wave and disappearance of the S wave, the ST segments become more depressed with inspiration.

FIG. 3. Case 771, 50 years, sthenic, recent myocardial infarct, no digitalis. Lead III. The most striking change with inspiration is the inversion of the T wave, which at first is upright. There is a slight initial increase in rate with subsequent slowing before expiration.

TABLE III

Type and Frequency of Respiratory Changes in Abnormal Electrocardiograms with Reference to the Presence or Absence of Digitalis Effect

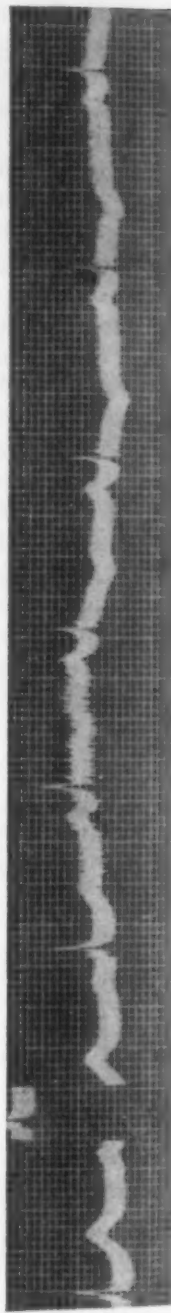| | | Digitalis | | | No Digitalis | | | | |
	L.A.D.	T.P.H.	Norm. Axis	L.A.D.	T.P.H. and Myo. Dam.	L.A.D. and Myo. Dam.	R.A.D. and Myo. Dam.	Norm. Axis and Myo. Dam.	Acute Myo. Infarct.
Number of Cases	116	33	131	237	145	344	39	548	76
Lead III									
VOLTAGE Increase	6.9%	36.4%	42.7%	11.8%	23.4%	9.9%	2.5%	33.4%	18.4%
Decrease	59.5	57.8	16.0	64.1	58.6	53.8	7.6	33.4	42.1
Q AMP. Increase	—	—	—	1.3	—	—	—	—	1.3
Decrease	23.3	18.2	9.2	21.9	9.7	19.8	—	12.0	18.4
Disappear	3.4	24.2	6.1	2.1	35.2	1.7	—	8.8	11.8
Appear	—	—	—	—	—	—	—	—	—
R AMP. Increase	37.1	87.9	50.4	28.3	80.0	30.8	2.5	49.1	42.1
Decrease	—	—	1.5	3.4	—	2.9	7.6	7.7	3.9
Disappear	—	—	—	—	—	—	—	—	—
Appear	4.3	21.2	2.3	2.5	22.1	2.6	—	3.5	5.3
S AMP. Increase	1.7	—	—	7.2	—	2.9	—	2.2	2.6
Decrease	39.7	48.5	16.0	38.4	30.3	37.8	—	19.7	21.8
Disappear	—	12.1	3.1	—	6.9	—	—	1.8	2.6
Appear	—	—	1.5	1.7	2.8	—	—	1.3	—
T AMP. Increase	2.6	3.0	—	16.0	11.7	4.4	—	4.9	2.6
Decrease	6.9	—	3.8	3.0	4.8	4.7	2.5	3.3	10.5
Incr. Positivity	4.3	12.1	3.8	44.3	28.3	14.0	—	14.0	3.9
Incr. Negativity	4.3	3.0	2.3	4.6	6.2	3.5	—	3.9	19.7
P AMP. Increase	11.2	9.1	6.1	15.6	16.6	11.0	—	13.3	18.4
Decrease	4.3	3.0	1.5	3.8	2.1	2.0	—	2.6	2.6
Incr. Positivity	19.0	12.1	9.9	27.9	28.8	20.4	—	22.0	30.2
Incr. Negativity	4.3	3.0	2.3	4.6	6.2	3.5	—	3.9	3.9
Lead CF IV									
VOLTAGE Increase	19.0	12.1	12.2	22.8	16.6	14.2	5.1	13.0	13.2
Decrease	25.0	27.3	26.7	30.8	33.1	29.4	5.1	35.4	23.7
Q AMP. Increase	6.9	—	3.8	—	—	4.4	—	1.6	3.9
Decrease	—	—	2.3	—	—	2.6	2.5	2.0	3.9
Disappear	—	—	1.5	—	—	1.7	—	1.5	—
Appear	1.7	—	1.5	—	1.4	1.2	—	1.5	—
R AMP. Increase	15.5	9.1	6.9	19.4	13.8	10.2	2.5	8.8	7.9
Decrease	23.3	18.2	22.9	30.0	30.3	26.7	5.1	32.5	22.4
Disappear	1.7	—	—	—	—	—	—	1.1	—
Appear	—	—	—	—	—	—	—	—	1.3
S AMP. Increase	6.0	6.1	7.6	8.0	12.4	6.4	2.5	10.2	9.2
Decrease	10.3	12.1	10.7	13.1	6.2	10.8	2.5	10.4	5.3
Disappear	1.7	—	—	—	—	—	—	1.1	—
Appear	—	—	—	—	1.4	—	—	—	—
T AMP. Increase	1.7	3.0	3.8	5.5	7.6	2.6	2.5	5.5	3.9
Decrease	4.3	3.0	—	10.1	9.0	7.6	5.1	8.6	3.9
Incr. Positivity	8.6	6.1	5.3	7.2	11.7	10.2	5.1	13.5	13.2
Incr. Negativity	7.8	3.0	—	11.4	12.4	9.6	7.6	11.9	3.9

In Lead III of the "digitalis group," the P waves increased in positivity in 44 cases (14.8 per cent) and increased in negativity in nine cases (3.0 per cent). In similar fashion, the QRS waves showed a marked tendency toward increase in positivity with inspiration. T_3, on the other hand, increased in negativity in 37 (12.4 per cent) and in positivity in 14 cases (4.7 per cent). The negative effect on the T wave fits with the well known

tendency of digitalis to lower or invert T waves (figure 2). In Lead III of the "no digitalis" group, the preponderant effect of respiration was to produce positivity of all deflections except for the subgroup of acute myocardial infarction. Apparently the presence of myocardial damage, unless acute, does not influence the direction of respiratory changes in the electrocardiogram. In the records of acute myocardial infarction, totaling 76 cases, 18 (23.6 per cent) showed a definite respiratory effect on the T waves. Fifteen presented increase in negativity and three increase in positivity of the T waves (figure 3).

In Lead CF IV of the "digitalis group," the R waves decreased in amplitude in 68 cases (22.8 per cent) and increased in 32 cases (10.7 per cent). The S wave decreased in 32 cases (10.7 per cent) and increased in 19 records (6.4 per cent). There was increased positivity of T waves in 19 cases (5.4 per cent) and increased negativity in 11 cases (3.7 per cent). Q wave changes with inspiration were few, but in 14 cases there occurred increase and in three cases decrease in amplitude. The respiratory changes in this group differ from the normal records chiefly in that the T wave tended to increase in amplitude in the digitalis cases but to decrease in the normal records.

In Lead CF IV of the "no digitalis" group, the most frequent effect on the T wave was a decrease in the amplitude of an upright deflection. This occurred in 120 cases (8.2 per cent). An upright T wave was increased in amplitude in 70 cases (4.8 per cent), but if to this group are added 37 cases in which diphasic T waves became upright (figure 4), 10 cases in which inverted T waves became upright, 14 cases in which inverted T waves became isoelectric, 11 cases in which inverted T waves became diphasic, and 17 cases in which there was decrease in the degree of inversion of the T waves, there is a total of 159 cases (11 per cent) in which inspiration tended to increase the positivity of T in CF IV.

In the group without digitalis effect, the respiratory changes were similar to those in the digitalis group, but it is interesting that in the fourth lead respiration was associated with increasing positivity of the T wave in cases of acute myocardial infarction. In two such records an inverted T wave became upright with inspiration. In comparing the respiratory changes of the abnormal electrocardiograms with the normal electrocardiograms, it would appear that the underlying myocardial damage was the factor responsible for the differences.

The effect of respiration on the rate in the digitalis group (table 2) was revealed by the production of slight sinus arrhythmia in 77 cases (25.9 per cent), moderate sinus arrhythmia in 18 cases (6.0 per cent), and marked sinus arrhythmia in three cases (1.0 per cent). The appearance of sinus arrhythmia was less frequent than in the normal group. The effect on the mechanism in the digitalis group was shown by the occurrence of auricular premature contractions in six cases, ventricular premature contractions or aberrant ventricular complexes in 18 cases, second degree auriculoventricular
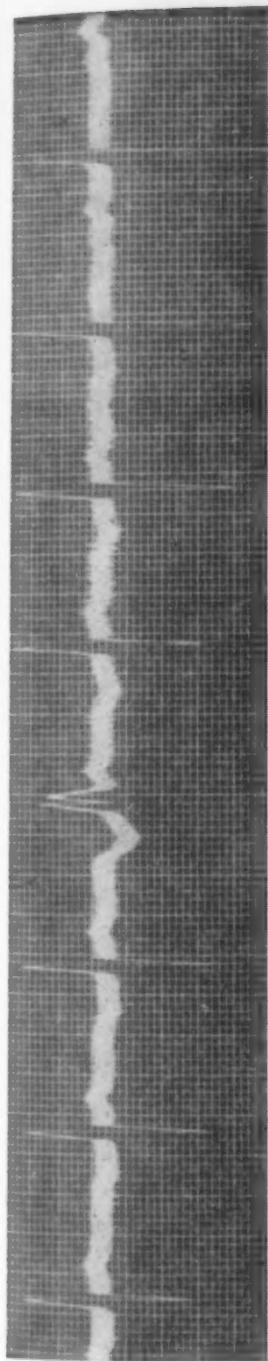
Fig. 4. Case 1740, 58 years, hypersthenic, hypertensive, cardiovascular disease, no digitalis. Lead CF IV. Record demonstrates decrease in amplitude of R and S waves, inversion of P waves and the change from diphasic to upright T waves. The rate is regular except for a fusion beat.
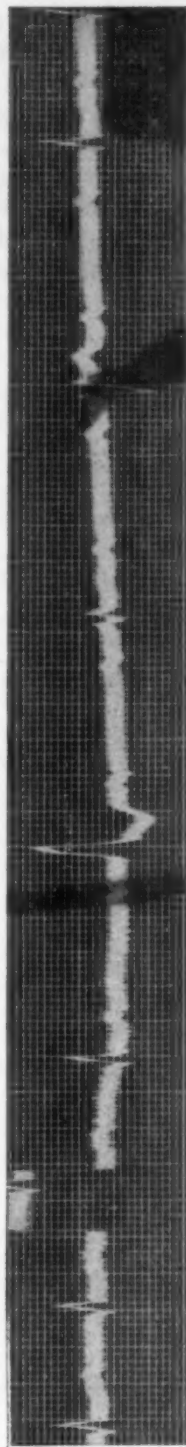
Fig. 5. Case 418, 69 years, sthenic, degenerative heart disease, digitalis. Lead III. Record shows prolonged PR interval which, with inspiration, shows increase in the auriculoventricular block from first degree to 2:1 with aberrant ventricular beats.
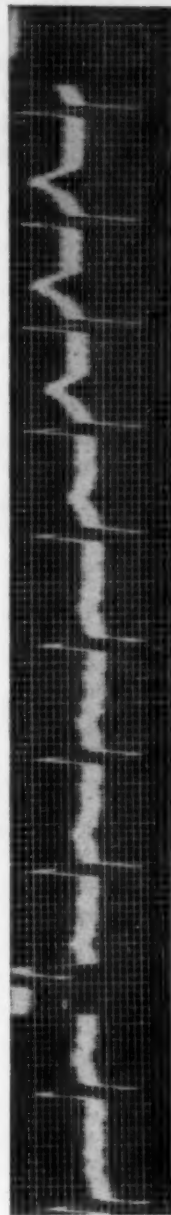
Fig. 6. Case 943, 22 years, sthenic, dermatitis, no digitalis. Lead CF IV. In this tracing there is increase in the depth of the S wave, and a change from a low amplitude m-shaped T wave to an upright T wave.

block in six cases, and a fusion beat, a sinus pause, a nodal escape and a ventricular escape in four instances (figure 5). The occurrence of ectopic beats was more frequent in the abnormal (9.4 per cent) than in the normal records (1.7 per cent). In the "no digitalis" group, inspiration caused slight sinus arrhythmia in 513 cases (35.7 per cent), moderate sinus arrhythmia in 194 cases (13.5 per cent), and marked sinus arrhythmia in 20 cases (1.3 per cent). Ectopic beats occurred in 62 cases.

The data in table 4 are divided into subgroups based on the presence of arrhythmias and include respiratory changes in records of some of the patients on digitalis, and some receiving no digitalis but having electro-

TABLE IV

Type and Frequency of Respiratory Changes in Abnormal Electrocardiograms
With Reference to Arrhythmias

|	Subgroups	Sinus Tachy.	Sinus Brady.	Auric. Fib.	Auric. Fib. and A-V Block	Auric. Flut.	A-V Block (More than 1st degree)	Misc.
	Number of Cases	167	143	87	9	8	8	107
LEAD III	VOLTAGE Increase	63.5%	34.3%	24.7%	55.5%	12.5%	37.5%	38.3%
	Decrease	29.3	46.9	28.4	—	—	25.0	17.8
	Q AMP Increase	—	—	—	—	—	—	—
	Decrease	12.6	6.3	13.6	—	—	—	7.5
	Disappear	5.4	17.5	8.6	11.1	—	—	7.5
	Appear	—	—	—	—	—	—	—
	R AMP Increase	47.3	57.3	43.2	55.5	25.0	50.0	44.9
	Decrease	6.0	8.4	1.2	—	—	—	7.5
	Disappear	—	—	—	—	—	—	—
	Appear	2.4	9.1	4.9	11.1	—	—	1.9
	S AMP Increase	2.4	3.5	2.5	—	—	—	3.8
	Decrease	16.2	31.5	19.8	—	12.5	37.5	6.5
	Disappear	1.8	2.8	1.2	11.1	—	—	1.9
	Appear	1.2	1.4	2.5	—	—	—	—
	T AMP Increase	6.0	14.7	1.2	—	—	—	13.1
	Decrease	5.4	5.6	—	—	—	—	7.5
	Incr. Positivity	20.4	32.9	7.4	11.1	—	—	25.2
	Incr. Negativity	8.4	10.5	3.7	—	—	12.5	10.3
LEAD CF IV	VOLTAGE Increase	19.8	13.3	4.9	22.2	—	—	19.6
	Decrease	29.9	49.0	22.2	11.1	50.0	37.5	38.3
	Q AMP Increase	1.8	1.4	—	—	—	—	—
	Decrease	1.8	2.8	—	—	—	37.5	—
	Disappear	1.8	—	—	—	—	—	—
	Appear	—	1.4	2.5	11.1	—	—	—
	R AMP Increase	13.8	11.9	2.5	—	—	—	13.1
	Decrease	24.0	45.5	17.3	—	50.0	—	34.6
	Disappear	—	1.4	2.5	11.1	—	—	—
	Appear	—	—	—	—	—	—	—
	S AMP Increase	13.8	18.9	6.2	11.1	—	—	13.1
	Decrease	12.0	11.2	13.6	11.1	—	—	8.4
	Disappear	—	2.1	2.5	11.1	—	—	—
	Appear	1.2	—	—	—	—	—	—
	T AMP Increase	—	7.7	1.2	22.2	25.0	—	3.7
	Decrease	7.8	14.7	1.2	—	—	—	11.2
	Incr. Positivity	8.0	11.9	3.7	22.2	37.5	12.5	4.7
	Incr. Negativity	10.2	15.4	1.2	—	—	—	15.0

cardiographic evidence of myocardial damage.   In this group of arrhyth-
mias, inspiration showed a tendency to increase the positivity of all deflec-
tions in Lead III and to do so in approximately the same proportions as in
the normal group.   However, there was a tendency for inspiration to result
in an increase in the amplitude of R waves, a decrease in amplitude of S
waves, and an increase in positivity of T waves more frequently with slower
rates.   This was shown by comparison of the per cent of R, S and T wave
changes in the sinus tachycardia and sinus bradycardia subgroups.   In the
latter subgroup, the T wave changes with inspiration were more numerous
and distinct than in records at more rapid rates; the T wave increased in
positivity in 47 cases (32.9 per cent) and increased in negativity in 15 cases
(10.5 per cent), including three cases in which a diphasic T became upright
and one case in which an upright T became inverted.   In Lead CF IV of
the "arrhythmia" group, changes in the Q wave were infrequent and showed
no predominating tendency toward positivity or negativity.   The R and S
waves tended to approach the isoelectric line, and the T wave changes were
approximately divided between increase in positivity and increase in nega-
tivity.   T wave changes occurred in 102 cases (19.2 per cent).   Ectopic
beats occurred with inspiration in too few cases of this group to be significant
but were more frequent in cases of sinus tachycardia than in sinus brady-
cardia.   Sinus arrhythmia in the sinus bradycardia subgroup was slight in
58 per cent, moderate in 18 per cent, and marked in 1.4 per cent of these
cases.

DISCUSSION

Several factors play some part in producing respiratory changes in
electrocardiographic tracings and should be mentioned.   The transverse
position of the heart, with its typical electrocardiogram, is well established,[10]
and the mechanical effect of displacement and rotation of the heart is em-
phasized by Lyle.[14]   If all changes were the result of simple gross shifting
and/or rotation of the heart, atropine or sympathetic stimulation would not
be expected to abolish these changes.[6]   The occasional similarity of respira-
tory and digitalis effects on the electrocardiogram suggests nervous in ad-
dition to mechanical factors.[2, 4]   Since there is frequently a change in direc-
tion of the QRS complex without significant change in the T wave of the
transverse heart with inspiration, it may be that a different or supplementary
factor is involved in the T wave changes when they do occur.   As shown in
table 3, inspiration caused changes in the T waves in 67 of 178 cases with
transverse position of the heart, while the other 111 cases showed no
T wave changes despite the shift from left to normal axis.   This suggests
independence of causative factors.   Scherf[20] suggested that a change in
heart rate might cause T wave changes which seemed to be related to
changes in the filling of the heart chambers.   It is true that in most cases
inspiration is closely associated with two or three quick beats which are
followed by a slowing of the rate before the expiratory phase occurs, and

it is known that inspiration increases venous return to the right heart. That change in rate is not the most important factor is shown by the changes in T waves in records with little or no sinus arrhythmia (figure 6). As stated previously, the records of sinus bradycardia in this report show relatively more frequent T changes and relatively more marked sinus arrhythmia than in the more rapid rates. Otto [17] demonstrated T wave changes by altering intraventricular pressures in dogs, and Lauson [21] demonstrated in man the definite increase in "net" pulmonary arterial pressure and the slight but definite decrease in "net" systemic arterial pressure with inspiration. He also showed a concurrent slight decrease in stroke volume of the left ventricle and a slight increase in stroke volume of the right ventricle. These observations would tend to support Otto's suggestion that a shift of the interventricular septum with inspiration might account for the T wave changes. Such factors could play a part in the T wave changes with respiration in human electrocardiograms.

Another factor in respiratory changes in electrocardiograms is the shunting effect of different tissues between the heart and the electrode as shown by Katz. Miller and Dent [22] explained the T wave as a manifestation of electrokinetic phenomena in which electrical energy is converted from mechanical energy by systolic contraction of the heart in "wringing out" the extracellular and intracellular fluid as well as coronary blood. Any change in coronary flow occasioned by inspiration would tend to alter the "streaming potentials" and hence change the T wave contour. There is evidence [23] that there are reflex changes in coronary blood flow subsequent to changes in venous return to the right heart. This is the so-called vagus coronary reflex, and is probably a part of the Bainbridge reflex involved in depression of vagal tone. A kinetic factor in the production of T waves might be accentuated by a sudden change in the anatomic relationships produced by inspiration. A final factor in the contour changes with inspiration is simply a change in position of the chest electrode in relation to the heart by the movement of the anterior chest wall.

The above factors are chiefly involved in changes of contour in electrocardiograms, but the reflex mechanisms also have an effect on the heart rate and cardiac mechanism, which may change with inspiration. The mechanical factors, such as movement of the diaphragm and possibly shift of the interventricular septum, do not directly affect the rate and rhythm, which we believe is mediated through nervous channels. Vagal effect is well shown in figure 5. Another conditioning factor is the decrease in peripheral arterial pressure with inspiration, by means of which the carotid sinus reflex may result in increased heart rate for a few beats. And, in like manner, inflation of the lungs stimulates pleural proprioceptors, with subsequent inhibition of the vagus center and increase in heart rate. There is probably also a central radiation of impulses from the cortex and/or the respiratory center to the vagal center.[28] This may be a relatively important

factor in rate changes in this series in which the patient is complying with a request to take a deep breath.

SUMMARY AND CONCLUSIONS

The effect on the electrocardiogram of a single deep inspiration during Lead III and Lead CF IV has been studied. An initial increase in rate followed by slowing of various degrees frequently occurred, but in very few instances was it possible to demonstrate changes in the auriculoventricular conduction with the changes in rate. Digitalis was associated with the most striking changes in rhythm, including usually a shift of the pacemaker from the sinoauricular node toward the auriculoventricular node, but the depression of the pacemaker also occurred in the absence of digitalis.

Numerous changes, including variations in contour of P waves, QRS complexes, and T waves in Lead III, were almost as frequent in normal as in abnormal records. The QRS complexes usually returned to their original configuration very shortly after the T waves assumed their previous form.

In Lead III of "normal records" there was a decided tendency for inspiration to result in increasing positivity of all deflections, but in Lead CF IV there was a tendency for inspiration to cause increasing negativity of all deflections. In abnormal electrocardiograms, except in cases of acute myocardial infarction or when the subject was under digitalis therapy, inspiration tended to increase the positivity of all deflections in Lead III. In the cases who received digitalis, or who had acute myocardial infarction, inspiration during Lead III tended to increase the negativity of the T waves, with an opposite effect on the other deflections. The frequency of T wave changes in Lead CF IV with inspiration detracts from the significance of the T wave in the interpretation of borderline records.

Respiratory effects on the electrocardiogram include changes in axis, in T waves and in cardiac mechanism. It has been suggested that the axis changes are the result of extracardiac factors, and T wave changes the result of intracardiac factors, and that variations in cardiac mechanism are the result of nervous reflexes, chiefly vagal.

BIBLIOGRAPHY

1. Einthoven, Rotherberger, and Winterberg; quoted by Woodruff, L. W.: A clinical study of respiratory variations in the form of the electrocardiogram, Am. Heart J. 8: 412, 1933.
2. Wilson, F. N.: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, Arch. Int. Med. 16: 1008, 1915.
3. Wilson, F. N.: Three cases showing changes in the location of the cardiac pacemaker associated with respiration, Arch. Int. Med. 16: 86, 1915.
4. Cohn, A. E., and Raisbeck, M. J.: An investigation of the relation of the position of the heart to the electrocardiogram, Heart 9: 311, 1922.
5. Resnik, W. H., and Lathrop, F. W.: Changes in heart rhythm associated with Cheyne-Stokes respiration, Arch. Int. Med. 36: 229, 1925.

6. Meek, W. J., and Wilson, A.: The effect of changes in position of the heart on the QRS complex of the electrocardiogram, Arch. Int. Med. 36: 614, 1925.

7. Doxiades, L.: Electrocardiogram in newborn before and after beginning of respiration, Abstract, J. A. M. A. 86: 1490, 1926.

8. Katz, L. N., Gutman, I., and Ocko, F. H.: Alterations in the electrical field produced by changes in the contacts of the heart with the body, Am. J. Physiol. 116: 302, 1936.

9. Edeiken, J., Wolferth, C. C., and Wood, F. C.: Upright or diphasic T wave in Lead IV as the only definite electrocardiographic abnormality in adults, Am. Heart J. 12: 666, 1936.

10. Sorsky, E., and Wood, P.: The use of chest leads in clinical electrocardiography, Am. Heart J. 13: 183, 1937.

11. Master, A. M.: The electrocardiogram and x-ray configuration of the heart, ed. 2, 1939, Lea and Febiger, Philadelphia, pp. 37–53.

12. Hernandez, A. G.: Evaluation of electrocardiographic accidents in Lead III during inspiration, Rev. cubana de cardiol. 4: 108, 1943.

13. Mazer, M., and Reisinger, J. A.: Deep Q_3 electrocardiograms, criteria for differentiating normal from cardiac subjects, Am. J. M. Sc. 206: 48, 1943.

14. Lyle, A. M.: Further observations on the deep Q_3 of the electrocardiogram, Am. Heart J. 28: 199, 1944.

15. Easby, M. H.: Electrocardiogram in four and a half month fetus, Am. Heart J. 10: 1, 1934.

16. Taylor, S. T.: The influences of pneumothorax on electrocardiographic findings, U. S. Vet. Bur. Med. Bull. 5: 850, 1929.

17. Otto, H. L.: The effect of sudden increase in the intracardiac pressure upon the T wave of the electrocardiogram, J. Lab. and Clin. Med. 14: 643–645, 1929.

18. Woodruff, L. W.: A clinical study of respiratory variations in the form of the electrocardiogram, Am. Heart J. 8: 412, 1933.

19. White, P. D.: Heart disease, ed. 3, 1945, The Macmillan Co., New York, pp. 7, 8.

20. Scherf, D.: Alterations in the form of the T waves with changes in the heart rate, Am. Heart J. 28: 333, 1944.

21. Lauson, H. D., Bloomfield, R. A., and Cournand, A.: The influence of the respiration on the circulation in man, Am. J. Med. 1: 4, 1946.

22. Miller, J. R., and Dent, R. F.: A new hypothesis of the production of the T wave in the electrocardiogram based on electrokinetic phenomena, J. Lab. and Clin. Med. 28: 168, 1942.

23. Best, C. H., and Taylor, N. B.: The physiological basis of medical practice, ed. 3, 1943, Williams and Wilkins, Baltimore, pp. 350, 468, 570.

CLINICAL NOTES ON AN EPIDEMIC OF POLIOMYELITIS *

By NED M. SHUTKIN, M.D.,† *Gastonia, North Carolina*

THE epidemic of anterior poliomyelitis in North Carolina during the summer months of 1948 was unprecedented both as to the number of cases and also as to the percentage of the bulbar and/or respiratory cases. The unusual incidence of the latter so taxed the facilities of the poliomyelitis unit set up at the North Carolina Orthopedic Hospital that, for the most part, we were obliged to admit only those patients with bulbar and/or respiratory symptoms and those with evidence of high spinal cord involvement, so frequently the precursor of respiratory or bulbar paralysis.

In the course of handling 362 acute cases, certain observations were made. Some of these, seen with a certain degree of constancy, either do not appear in or are at variance with the contents of the discussions on poliomyelitis appearing in the standard textbooks and key articles. An attempt was made, insofar as our limited diagnostic facilities and acumen permitted, to analyze each case physiologically and to prescribe treatment accordingly.

The patients were given a complete physical examination when first seen to determine, insofar as possible, the correct diagnosis. Among the patients referred with a presumptive diagnosis of poliomyelitis were found cases of tick paralysis, Guillain-Barré syndrome, rheumatic fever, acute rheumatoid arthritis, mumps, subdeltoid bursitis, transient epiphysitis of the hip, heat stroke, pneumonia, emotional syncope, upper respiratory infections and hysteria. Many other patients in whom disease was either not present or not detected were also seen. In fact, one of the local poultry raisers requested we treat his chickens for limberneck, quite conceivably also a virus infection of the nervous system. Of the above mentioned conditions, tick paralysis was perhaps the one in which error could most easily be committed. Those patients who did not describe the typical "dromedary" course of onset, who had a negative spinal tap and who were a bit on the dirty side were subjected to a thorough search of all integument, so as not to miss an offending tick. Our efforts were rewarded in two instances. It must be remembered that if the tick is not removed, the paralysis may be fatal.

A spinal tap was done in all but five cases with acute poliomyelitis, irrespective of the presence of paralysis and the virtual certainty of the diagnosis, inasmuch as in some instances a significant increase in cerebrospinal

fluid pressure was noted, as high as 450 mm. of water, which was felt to be
contributing to the clinical picture.   The pressure was reduced by graduated
drainage, and the procedure was repeated subsequently as often as necessary.
The likelihood of a negative spinal tap in acute poliomyelitis was not sup-
ported by our findings.   Of the 357 cases tapped, only one had a negative
spinal fluid.   The question naturally arises as to what constitutes a positive
tap.   Without any hard and fast rules, we considered 10 cells as borderline.
If the Pandy test was positive, we considered the tap positive.   It should
be noted, however, that there were exceedingly few instances in which the
spinal fluid findings were and remained equivocal.   It should also be noted
that there was no parallel between the intensity of the spinal fluid findings
and the severity of the disease.   In the great majority of cases, the cell
count was between 20 and 200, with polymorphs predominating early, being
replaced by lymphocytes in 24 to 48 hours.   In two cases, seen in the pre-
paralytic stage, the fluid was turbid as the result of a cell count in the
neighborhood of 1,000, with polymorphs predominating.   Definite diagnosis
had to await the onset of paralysis, replacement of the polymorphs by
lymphocytes, and a therapeutic test of penicillin.

As a rule, the onset of the disease was characterized by the aforemen-
tioned "dromedary" course, consisting of a day or two of fever, malaise,
upper respiratory and/or gastrointestional symptoms; spontaneous sub-
sidence of these symptoms for another day or two, followed by recurrence
of these symptoms, usually in a more severe form and accompanied by
headache, nuchal rigidity, muscle tightness and soreness, and possibly
paralysis.   The subsequent clinical course ran no fixed pattern.   The se-
verity of the prodromal symptoms, the level of fever, the spinal fluid findings,
the degree of nuchal rigidity and muscle tightness could in no way be con-
sidered as indices to the severity or the locale of any impending paralysis.
Many writers have commented on the rôle of fatigue incurred during the
prodromal phase as an augmenter of the severity of the disease.   Although
we have no statistics, our observations would support this contention.   This
gives rise to an interesting conjecture, however.   In poliomyelitis, the dif-
fuse involvement of the brain as well as of the cord, irrespective of the
absence of bulbar symptoms, is acknowledged.[1,2]   And it is conceivable
that in the case predestined to be severe, cerebral irritation may induce the
fatiguing activity, with the latter being the result of, rather than a contribu-
tor to, the severity of the disease.   It was impossible to prophesy the extent
to which paralysis would develop, the duration of the acute phase during
which paralysis could develop, or the degree of recovery.   Because of this
unpredictability, it was found advisable to give each case a guarded initial
prognosis until the acute phase had passed, which, in some cases, took 10
or more days.

Contrary to some opinion, there is not necessarily any immunity to polio-
myelitis during the first six months of life.   We had 10 cases within that
age group, three of which were under eight weeks old.   As might be ex-

pected, the prognosis in these infants is not as good as in older children with the disease of comparable severity.   This brings up the point that poliomyelitis is a systemic disease, with possible cardiac, pulmonary and gastrointestinal elements that must be sought for and handled.

In the interest of clarity, the cases will be discussed according to their classification as spinal, respiratory or bulbar, with full realization that many fell into two and even three of these categories.   In the latter event, therapy was directed primarily toward the more critical considerations.

Those cases with only spinal paralysis were put to bed, kept comfortable with analgesics and barbiturates if necessary, and given physical therapy as early as possible but not until it could be done without adding to the patients' discomfort.   The controversies raging among the physical therapists as to the advisability of immediate or deferred stretching, gentle or forceful stretching, or the use of hot packs are so many storms in teacups.   Approaching the subject on the basis of rational physiology, it should be obvious that stretching a tight muscle, be it early or late, could not possibly alter a disease process located in the spinal cord.   Furthermore, the precise reason for stretching must be appreciated.   One must differentiate between the contraction of the presumably spastic muscle in the acute phase and the contracture of the noncontractile connective tissue in and about the muscle following the acute phase.   It is no more reasonable to expect stretching of the contracted muscle in the acute phase to produce relaxation of the muscle than it would be reasonable to expect relaxation of a spastic muscle from stretching in a case of cerebral palsy.   Hence it becomes obvious that the only valid reason for stretching a tight muscle in the acute phase is to obviate subsequent contracture of the noncontractile connective tissue elements in or about that muscle.   It was our experience that no contractures developed from gentle, unhurried muscle stretching done at a time and at a pace that did not increase the patient's discomfort.

Hot packs were used only sparingly, for several reasons.   In the first place, a hot pack program carried out according to protocol would have completely usurped the time and efforts of the insufficient personnel, who were taxed to the utmost taking care of the direly ill bulbar and respiratory cases.   Secondly, the great majority of uncomfortable patients obtained prompt and adequate relief from judicious doses of aspirin and phenobarbital. Thirdly, it was deemed inadvisable to subject our acutely ill patients, so many of them under three years of age, to the additional exhaustion, dehydration and electrolyte depletion attendant upon a full-scale hot pack program, particularly during the hot summer months.   Most important of all, however, is the fact that hot packs were not necessary.   As previously stated, physical therapy prevented contractures, with only aspirin and phenobarbital to allay the discomfort.   In a few instances where muscle soreness and tightness were extreme, even to the extent of producing opisthotonus, hot packs were employed and, true enough, were effective in relieving the tightness, but only during the period they were applied.   Following

removal of the packs, the tightness promptly returned, and to a degree comparable to that present prior to application of the pack; nor was there any evidence indicating that the use of hot packs shortened the duration of the tightness.

Following subsidence of the acute stage, therapy was directed toward three objectives: prevention of fixed contractures; strengthening, insofar as possible, surviving muscle elements, and coördination of residual and substitute motion. Position of function was maintained, insofar as possible, by means of sand bags, foot boards, shoe bars, pillows, slings and other gadgets designed to fit the individual requirement. This aspect of convalescent care cannot be too strenuously enforced. It is folly to expect a convalescent but otherwise healthy child to remain immobile in any fixed position for days on end. As long as adequate daily physical therapy maintained suppleness in the soft tissues, no deformities occurred. Braces were employed as early as feasible, not so much to obtain immobilization as to allow mobilization. It was felt that active use of weakened muscles while supported in a position of mechanical advantage abetted the strengthening process. Plaster casts were used infrequently, and only in those few cases where deformities occurred or seemed imminent as a result of muscle imbalance that defied the efforts of the physical therapist. Although not so deplorable as soft tissue contracture in the position of deformity, contracture in the position of function, plus the disuse atrophy of surviving muscle elements from prolonged plaster immobilization, certainly is not much more desirable.

The various drugs that have been prominent in the literature were tried. No relief of muscle tightness was obtained from Neostigmine. Thiazolyl and para-aminobenzoic acid gave no evidence of either forestalling or minimizing paralysis. Furmethide was used in the recommended doses for urinary retention, and was successful in all cases. In that regard, it is of interest to note that we saw one patient who had a typical history, general physical findings and positive spinal tap indicative of poliomyelitis, and who had bladder paralysis but no other detectable paralytic findings.

The general rule governing the handling of cases with respiratory paralysis was to supply, by one means or another, an adequate oxygen intake, and then to wean them as soon and as rapidly as feasible. In those cases of relatively mild diaphragmatic and/or intercostal involvement, nasal oxygen was employed in an effort to obviate the use of the respirator. This is desirable, if possible, since the weakened muscles do not undergo disuse atrophy resulting from the usurpation of their function by the iron lung. However, if mere nasal oxygen proves inadequate in these mild cases, or if the respiratory weakness is of any moment, the respirator should be used promptly. The necessity for the use of the respirator should not be indicated by dyspnea, cyanosis and the other dramatic signs of acute air hunger, but rather by the more subtle signs such as dilatation of the alae

nasae, abdominal breathing, diminished thoracic excursion, staccato speech, and even barely perceptible dulling of the sensorium.

That a state of hypoxia may come on insidiously rather than violently, with gradual rather than sudden diminution of atmospheric oxygen tension, as is the case with progressively increasing respiratory weakness, has been amply proved by high altitude studies. According to Best and Taylor [3] : "When the altitude is less than that which causes loss of consciousness, the aviator may at first experience sensations of excitement, exhilaration and well-being. With the attainment of higher altitudes, effects of a more serious nature develop, often insidiously."

Observations on high altitude flying during the war showed that hypoxia could produce loss of consciousness, not necessarily with a preceding stormy phase of dyspnea and cyanosis. With this in mind, it must be appreciated that a significant degree of hypoxia may be present from what may be erroneously considered only mild respiratory impairment, and, further, that this hypoxia over a sustained period may produce irreversible damage to the vulnerable nervous tissues.[3] Consequently, it is imperative that the presence of hypoxia be detected, and the respirator promptly used, provided nasal oxygen alone proves inadequate. Not infrequently the presence of hypoxia is manifested only by lassitude, fixity of ideas, slight impairment of alertness, a mild state of excitation, unwillingness to speak or inability to complete a sentence without taking a breath. Immediate use of the respirator will confirm the impression. The wisdom of such a procedure in our cases presenting these signs was amply attested to by the prompt restoration of alertness. Shortly after this, the patients would invariably lapse into a long and deep sleep, testimony of the accumulated fatigue from the effort, however masked, to maintain adequate oxygen intake. We had one patient initially thought to be a case of polioencephalitis, admitted in deep coma, who did not recover consciousness for seven weeks, but whose coma, in retrospect, was felt to have resulted from a 48 hour period of hypoxia prior to admission rather than from involvement of the cerebrum by the virus.

It was noted that the majority of the patients with early evidence of high cord involvement, particularly weakness of the shoulder girdle muscles, went on to some degree of respiratory paralysis, usually requiring artificial respiration. Consequently, these patients were always admitted and carefully observed. This vigilance was of utmost importance, since several cases with paralyzed deltoids but with apparently intact respiratory musculature showed profound involvement of the latter within two or three hours of the initial examination.

As a rule, the respirator was set at a fairly rapid rate, which was progressively reduced as synchronization occurred. A variation of about 15 pounds of pressure was used, 10 pounds of negative pressure and five pounds of positive. The use of the positive pressure was felt to be important in the control of the pulmonary edema that frequently occurred with the sus-

tained use of negative pressure.   Referring back to physiologic principles, the presence of edema represents a disproportion between the intracapillary filtration pressure on one hand and the intracapillary osmotic pressure, plus the tension in the surrounding tissue spaces, on the other.   By establishing increased and sustained negative pressure in the pulmonary alveoli, the pressure in the septal tissue spaces is decreased, thereby impeding the normal reflux of tissue fluids back into the capillaries, with resultant tissue edema and transudation into the alveoli.   That this is not a mere academic consideration was indicated by the prompt elimination of the edema with the initiation of an element of positive pressure in the artificial respiratory force.

Weaning should be accomplished as soon as possible and in as short a period of time as possible.   Here individual judgment must be used.   If some elements of the respiratory musculature either survive or recover from the paralytic process, disuse atrophy stemming from prolonged, uninterrupted use of the iron lung must be avoided.   On the other hand, discontinuing artificial respiration in a patient with insufficient musculature will defeat its purpose.   At the outset of the weaning process, the respirator should be stopped with the collar released but without removing the patient. The patient must be under constant observation, and the artificial respiration must be resumed as the patient's tolerance is approached.   Those patients who are found able to breathe unaided, however temporarily, should be allowed to do so during daily, progressively increasing periods.   It is of utmost importance that from the beginning the patient have implicit confidence in the fact that artificial respiration will be resumed at any moment he may require it.   Otherwise the attendant apprehension and even panic obviously will increase the oxygen requirement and render a temporarily adequate respiratory musculature unable to cope with the increased demand.

Two other points are worthy of note.   One is the fact that during the weaning process, the ability of a given patient to remain out of the respirator for several consecutive hours on one day is not necessarily an indication that the same patient can remain out for a similar period the following day. The second is the fact that many patients who show appreciable return of function of the involved respiratory muscles will demonstrate a deep and rhythmic respiratory excursion following removal from the respirator, but will rapidly lose their ability to breathe unaided as fatigue sets in.   Hence, in both of the above cited instances, it is necessary to maintain close vigilance even in those cases where there has been appreciable recovery.

It must also be remembered that hypoxia may represent cardiac as well as respiratory impairment.   Consequently, those cases which persist in their constant requirement of the deep, rhythmic respiratory excursion provided by the iron lung, with or without nasal oxygen, despite what seems to be adequate recovery of respiratory function, should be investigated for the presence of an acute myocarditis.

A final note concerning the apparatus.   In any situation dealing with a number of respirator and bulbar cases, electric power is vital.   It is there-

fore imperative to have an auxiliary source in the event of failure of the conventional supply.   We purchased a 7,500 ampere gasoline generator which was hooked up directly to the wires from the city power lines, so that in the event of failure of the latter it was not necessary to change the wall plugs.   In our hospital, it was necessary to throw only a single switch and start the generator.   We found that a 7,500 ampere generator could easily provide power to operate six adult respirators.

A final point of warning concerns the care that must be exercised in regard to the floor wires.   During the more hectic phases of our epidemic, many yards of extension wire had to be laid on the floor to accommodate the many respirators, suction machines, lights, sterilizers and other electrical apparatus employed.   It was very easy, during the frequently intense activity about these critically ill patients, inadvertently to disconnect with one's shoe an extension cord, with the possibility of dire results if undetected.

A definite degree of concern must be continued in those cases that recover to an extent that permits permanent freedom from the use of the respirator but with residual weakness of the respiratory musculature.   These patients continue to be particularly vulnerable to disorders involving the respiratory tree, frequently precipitating an emergency.   Every effort must be made to prevent them from contracting infections and to control, insofar as possible, any preëxisting pulmonary disease.   Residual intercostal weakness, with its loss of forceful expiratory power to enable the patient to dislodge any mucus or foreign substance, is particularly unfortunate.   We had such a case, a three year old girl whose respiratory function had recovered to an extent that enabled her to indulge in routine activity without being in the respirator for three weeks, but who suddenly developed atelectasis of the right middle and lower lobes.   Bronchoscopy revealed copious amounts of mucus in the larger bronchi to these lobes, with appreciable mucosal edema, and the condition was relieved by aspiration through the bronchoscope.   Auscultation thereafter revealed sibilant râles throughout the chest, more pronounced on expiration and quite typical of bronchial asthma.   Interrogation of the parents yielded the hitherto unobtained information that the patient had had previous bouts of what the family doctor had called asthma. Consequently, the patient was kept in Trendelenburg's position in the respirator, with positive pressure to aid the drainage and disgorgement of the accumulated mucus.   However, one week later, despite progressive clearing of the lungs and diminution of the asthmatic attack, as determined by auscultation, the patient suddenly developed a massive collapse of the right lung and promptly died despite all resuscitative efforts.   It must be remembered that such an eventuality is a constant threat to all patients with any degree of residual respiratory paralysis, and the parents should be briefed as to both the possibilities and their prevention.

However important constant and intelligent vigilance is in cases of respiratory paralysis, it is even more so in the cases with bulbar involvement. It cannot be over-emphasized how easily and peacefully a bulbar case can

662 NED M. SHUTKIN

die of suffocation if unattended for only a few minutes. In those cases with involvement of only certain cranial nerves rostral to the glosso-pharyngeal and the vagus, watchful waiting suffices. These, of course, are not true bulbar cases. Unfortunately, only few of our patients fell into that category; the majority had involvement of the motor nuclei in the medulla, as well as respiratory, trunk and extremity paralysis. Several of our patients were paralyzed literally from the ears down.

The handling of those bulbar cases with involvement of the caudal cranial motor nuclei, as well as the medullary vital centers, is the most difficult problem confronting the physician and nursing staff. While it is true that in this epidemic most of the severely involved bulbars died irrespective of any heroic efforts, nevertheless certain procedures are indicated that in certain instances may enable a borderline case to survive. In evolving the routine of therapy in the individual case, an attempt was made to determine how the disease had altered the patient's normal physiology and, if at all possible, how those alterations could be eliminated or minimized.

The main contribution to the survival of the severe bulbar case is the maintenance of an adequate airway. Obstruction occurs from two sources: unaccommodated mucus and saliva in the pharynx, resulting from inability to swallow; and approximation of the vocal cords, from laryngeal paralysis. Here again the rôle of hypoxia must be considered. Hypoxia, of a clinically significant degree, can occur with only mild obstruction. Not only is the partial obstruction a deterrent to adequate pulmonary ventilation, but it rapidly gives rise to profound pulmonary edema, which very substantially encroaches upon the alveolar volume available for oxygen transfer. The prompt occurrence of pulmonary edema in obstruction results from the relatively negative intra-alveolar pressure induced by forceful inspiration with inadequate ingress of air, causing transudation of tissue fluids into the alveoli.

According to the textbooks and standard articles, avoidance of unaccommodated pharyngeal secretions is accomplished by postural drainage and suction. However, for the former to be effective, the patient should be kept on his side and the foot of the bed elevated sufficiently so that the patient makes an angle of at least 30 degrees with the horizontal. We found it necessary to lash the patient's feet to the foot of the bed.

Suction is an indispensable procedure but it has its hazards. Because of the frequency with which suction must be used to remove the constantly accumulating mucus and saliva, and because of the strength of the suction necessary to remove the ropy mucus, appreciable irritation of the mucosa results, with swelling, definitely increased secretion and even active bleeding. The swelling tends to encroach upon the caliber of the airway, and the increased secretion adds to the amount of fluid to be removed. The bleeding is especially unfortunate and adds immeasurably to the patient's jeopardy. It is difficult to stop because of the necessity for constant suction, and the formation of clots provides additional mechanical obstruction. On innum-

erable occasions, in such cases, aspiration through the glottis yielded large pieces of blood clot, not infrequently circular casts of the trachea. Therefore, in order to decrease secretion and thereby minimize the necessity for suction, a technic of controlled hydration was utilized and found to be highly successful. On admission, fluids were withheld until the patient no longer required frequent suction, and that degree of dehydration was maintained. It was found that, in this manner, patients could be carried with virtually no or merely occasional suction, and still be sufficiently hydrated to meet their metabolic requirements. Whatever secretions were present were handled by postural drainage and expectoration. This technic of limited hydration was found to be a valuable adjunct in treatment, not only because it obviated suction but also, and perhaps even more important, because it permitted the use of the respirator. According to prescribed treatment, the use of the respirator in bulbar cases is contraindicated, since it tends to force the patient to aspirate the pharyngeal secretions. This of course is true enough, but it does not occur when the pharynx is free of fluid. As long as the respirator can be used with impunity, it has a definite therapeutic rôle in these cases. With involvement of the respiratory center, the discharge of normal, rhythmic impulses to the muscles of respiration is interfered with, resulting in irregular, shallow, inadequate breathing despite intact respiratory musculature.[3] The use of the respirator to restore rhythmic respiratory excursions of adequate depth will frequently overcome the hypoxia occasioned by the inadequate breathing. Return of alertness and, occasionally, even of consciousness promptly followed placing the patient in the respirator. Here again, the same technic of obtained synchronization as previously noted was used. The range of pressure was also the same, about 10 pounds of negative and five pounds of positive. The use of the latter resulted in prompt elimination of the pulmonary edema which occurred with the slightest degree of obstruction.

Needless to say, nasal oxygen was promptly instituted to raise as high as possible the alveolar oxygen tension. This might have been better accomplished had an oxygen tent been used, but the tent was deemed impractical in view of the necessity of having the patient's head immediately accessible.

Tracheotomy is a life-saving procedure and, when indicated, should be done early. The prime indication for tracheotomy is pharyngeal or laryngeal obstruction to the airway, the former being caused by unaccommodated mucus and the latter by paralysis and approximation of the vocal cords. In both instances, hypoxia exists and, again, is abetted by the pulmonary edema that invariably occurs, making procrastination detrimental to the welfare of the patient. The presence of obstruction can be easily determined clinically. The cardinal signs are: the presence of mucus in the pharynx; approximation of the vocal cords, as seen on direct examination of the larynx with a laryngeal mirror; stertorous breathing; decrease in the peripheral breath sounds on aucultation; retraction of the intercostal spaces on in-

spiration, and the prompt development of pulmonary edema. In our series of cases, eight tracheotomies were done, all for laryngeal obstruction, since we were able to solve the problem of pharyngeal mucus by controlled hydration. In most of the cases, the vocal cords were visualized; in the remainder, technical difficulties prevented our doing so, but the other clinical signs established the indication for the tracheotomy. It should be noted that only one of the eight patients on whom this procedure was performed survived, but the seven fatalities all occurred at least 24 hours after the tracheotomy and none died as the result of suffocation.

The use of an O'Dwyer tube was considered as a substitute for tracheotomy, but consultation with a laryngologist [4] dissuaded us. The intubation requires the skill of a trained laryngologist, and one must be on hand at all times in the event the tube is coughed out, as frequently happens. Also, the tube cannot be left in for more than three or four days without setting up a reaction in the larynx which may, in itself, necessitate a tracheotomy for extubation.

Two conditions may simulate respiratory obstruction for which unindicated tracheotomy might be done. One occurs in polioencephalitis, in which the patient manifests the same type of stertorous breathing seen with other intracranial affections, but of cerebral origin. The absence of diminished breath sounds and pulmonary edema and auscultation over the larynx gives ample evidence that obstruction does not exist. The other occurs in acute myocarditis, where the dyspnea is due to myocardial insufficiency rather than to any obstruction.

The problem of maintaining fluid and electrolyte balance and nutrition merits discussion. For the most part, fluids were given by proctoclysis. This proved to be an admirable method. The ease of administration, the ability to maintain it for several days without any discomfort to the patient, and its undisturbed flow even in a patient who thrashed about rendered it superior for our purposes to intravenous or subcutaneous administration. It was a particularly efficient procedure in patients confined to the respirator. Absorption was prompt, due to the mildly dehydrated state of the patient, and in only a very few instances did the fluid act as an enema. We found it an excellent method of controlling hydration to decrease pharyngeal secretion. Glucose, usually 5 per cent, was given in either water or saline, depending upon electrolyte depletion from perspiration and/or vomiting. To abet the nutritional requirements, amino acid solution was given. This was usually administered subcutaneously, because of the difficulty in keeping a needle in the vein of a thrashing patient and because the solution was given very slowly over a period of many hours, so as not to too fully rehydrate the patient. The solution was promptly absorbed, and with no more discomfort than attends similar administration of saline solution. In one case a sterile abscess developed, which responded immediately to multiple aspirations and a pressure dressing. In cases requiring prolonged parenteral feeding, plasma was also administered as needed.

The use of gastric feeding via a Levine tube is to be condemned. In the first place, the tube is an irritant to the pharyngeal mucosa. In the second place, the gastric dilatation and the interference with peristalsis attendant to vagus paralysis results in the accumulation and stagnation of the high caloric fluids so regularly injected down the tube, and so unceremoniously and copiously vomited two or three days later. One is deluded into thinking that these fluids are supplying the metabolic needs, whereas actually very little gets beyond the pylorus. This was made dramatically apparent to us in several instances of severe respiratory embarrassment caused by pressure of the fluid-laden stomach against the diaphragm in patients in the Trendelenburg position, where complete relief was promptly obtained by aspiration.

A particularly lethal form of polio is the encephalitic variety, of which we had four cases, three fatal. These cases are distinguished clinically by a peculiar but characteristic appearance of apprehension and an involuntary jerkiness that usually progresses into a convulsion. This convulsive state may be severe, prolonged and recurrent. We attempted to control these with dilantin and barbiturates, with some success. It is difficult to determine the optimal dosage, since it is highly desirable to avoid the exhaustion resulting from a convulsion, and similarly desirable to avoid undue depression of the vital centers in the medulla, which may very likely be further compromised by the poliomyelitis virus. The three fatal cases apparently died from myocardial failure. The case that survived also had bulbar symptoms, and, incidentally, was also the only survivor of the eight cases that had tracheotomies. She is of interest for several reasons. In the first place, it cannot be definitely ascertained whether she represented a true case of polioencephalitis. She was admitted in coma, with evidence of mild respiratory obstruction for approximately 48 hours, and there is great likelihood that mild but sustained hypoxia rather than the virus was responsible for her coma. Secondly, she represented a remarkable recovery. She remained in coma for seven weeks, during which time she exhibited the severe rigidity ascribed to diffuse involvement of the various intracranial motor components. The consensus was that, if consciousness was ever regained, the patient would be a severe case of cerebral palsy. However, upon regaining consciousness, the patient showed rapid improvement. The tracheotomy tube was removed, with rapid healing ensuing. Although a slight amount of spasticity persisted, the patient had virtually no gross muscle dysfunction. Her phonation was not normal, although her speech was intelligible and improving. There was no intellectual impairment.

An insufficiently publicized consideration occurring in any condition with coma is the danger of an exposure keratitis from coma vigil. This possibility was anticipated in this patient, but no precautions other than observation were deemed necessary, since it was noted that she kept her eyes closed for several hours each day. However, during the fourth week of coma, the left eye apparently was uncovered for too long a period, and

an exposure keratitis developed and rapidly progressed to rupture and disintegration of the eyeball despite all efforts to prevent this. It should be noted that this eye had been damaged three years earlier when a scissors blade had been stuck into it, and conceivably this might have caused sufficient circulatory damage to make the eyeball unduly vulnerable. At any rate, the eye was lost, and it might not have been had we not been lulled into a false sense of security. The prescribed prophylaxis is to keep the eyes completely closed by pressure bandages, or even to suture the lids together with black silk if the former method is ineffectual.

The causes of death in bulbar poliomyelitis provoke some discussion. Death is routinely ascribed to the failure of the vital centers in the medulla, a vague statement which is not always substantiated clinically.

Half of our bulbar patients who died exhibited the classical clinical picture of peripheral vascular failure. There were the fall in blood pressure with the decrease in pulse pressure, rapid, thready pulse and cold, clammy, mottled extremities. These patients, despite the shocklike picture, did not respond to the routine therapy of vasopressor stimulants.

It is generally conceded that the vasomotor center, consisting of vasoconstrictor and vasodilator elements, is situated in the floor of the fourth ventricle just above the obex. A demonstration of the elimination of the dominant vasoconstrictor tone occurs in transection of the cord in the lower cervical region, with interruption of the stream of impulses from the medullary to the spinal centers resulting in vasodilatation and a fall in blood pressure. In this state of so-called spinal shock the blood may fall to a dangerously low level, but this is the exception rather than the rule, which tends to cast some doubt on the assumption that paralysis of the medullary vasomotor centers can be categorically ascribed as the cause of death. A further possibility is suggested by Best and Taylor [8]: "It is unlikely that these areas represent the highest centers of the vasomotor system. More recent work indicates that the latter are situated in the hypothalamus, and even in the cerebral cortex."

The other prominent vital center in the medulla, paralysis of which is also considered to be a major cause of death in bulbar poliomyelitis, is the respiratory center. This respiratory center is "a collection of nerve cells in the brain stem which discharge impulses to the muscles of respiration. . . . The respiratory center is connected with the motor neurones of the phrenic and intercostal nerves in the cervical and upper thoracic segments of the cord by descending tracts which run in the anterior columns and in the ventral part of the lateral columns of the spinal cord." [8] Inasmuch as the constant and regular discharge of respiratory impulses originates in this center, it is only reasonable to expect the profound alteration in respiration following its destruction, despite an intact respiratory musculature. On the other hand, there is no evidence that this center is involved in any other vital process. Consequently, it is also reasonable to expect that substituting a respirator which can establish and maintain an adequate and rhythmic res-

piratory excursion should obviate the threat to survival stemming from an impaired or defunct respiratory center.   However, the use of the respirator did not prevent death in those cases who showed respiratory center involvement, despite a patent airway, and who showed no clinical evidence of myocardial failure or peripheral vascular collapse.   In the light of this, we are obliged to amend our concept as to the lethal effects of paralysis of the respiratory center per se.

In probing further for the cause of death from poliomyelitis in those cases where measures obviating suffocation were instituted, the possibility arises of either higher intracranial vital centers or cardiac involvement, or both.   In consideration of the former possibility, Bodian,[1] in a detailed pathologic analysis of 24 cases of fatal poliomyelitis, showed that there was widespread involvement of the brain in each instance.   From a similar study of the brains in 22 fatal cases of poliomyelitis, McCarter[2] reports "constant involvement of the medulla, pons, and mid-brain, with more or less involvement of the basal ganglia, thalamus and hypothalamus."

Relative to the possibility of cardiac involvement, review of our 28 fatal cases indicated that half that number died from what appeared to us clinically to be acute myocardial failure.   The picture was that of sudden death with only a relatively short preterminal phase, characterized by a moderately rapid pulse of deteriorating quality, with no appreciable fall in blood pressure or rise in venous pressure.   This was succeeded in rather abrupt fashion by marked deterioration of the pulse and subsequent cessation of the heart beat.   Respiratory function was maintained throughout.

Perusal of the literature for corroboration of this clinical impression provided only scanty reports, concerned with the systemic pathology of poliomyelitis.   In 1945, Saphir[5] reported the autopsy findings of 17 cases of fatal poliomyelitis.   Acute myocarditis was found in 10 of these.   "The hearts were dilated, soft, and flabby.   The papillary muscles and chordae tendineae were flattened.   The myocardium invariably was pinkish gray or brownish gray, and of a boiled appearance, with loss of its normal architecture.   Petechial hemorrhages were often encountered in the endocardium and epicardium. . . . Microscopic examination of the myocardium disclosed myocarditis in ten instances.   In two, the inflammatory changes were very marked and diffuse; in six, they were more or less localized; and in two hearts, the changes were only slight.   In the first two hearts, the changes were so severe that there seemed to be a massive extravasation of leukocytes. Many polymorphonuclear leukocytes were encountered and many lymphocytes.   Red blood corpuscles were also present in the inflammatory exudate. Many heart muscle fibers were compressed by the exudate and appeared thinned out, while others were the seat of cloudy swelling.   There was no evidence of necrosis.   Both the right and left ventricles were involved. . . . The sudden death of some of these children can easily be explained by the myocarditis."

In this regard, it is of interest to note that, with one exception, we saw

no evidence of clinically detectable myocarditis in the cases with spinal paralysis alone, despite the profundity and widespread distribution of the paralysis. If systemic dissemination of the virus itself or of a toxin is responsible for the myocardial damage, it is reasonable to assume that similar damage could occur in those cases of severe spinal involvement. Only one such instance occurred. In this case, the patient was literally paralyzed from the neck down. Despite a patent airway, clear lung fields and satisfactory synchronization with the respirator, the constant administration of oxygen was necessary. The classical clinical signs of acute myocarditis were present. Digitalization was tried with no benefit. The patient continued to run a downward course and died three weeks after the acute onset.

The management of bulbar and respiratory cases requires certain indispensable equipment. Of primary importance are respirators of all sizes, and suction machines. Along with the respirators should be a supply of tracheotomy collars and bars, to permit the use of the respirator when indicated in cases where tracheotomies have been performed. The suction machines should be equipped with both rubber and metal suction tips of various sizes. Sterile tracheotomy sets, containing tubes of various sizes ready for immediate use, should be kept on the ward. It is wise to include a self-retaining retractor in the set, in the event of insufficient assistance, and an adequate light should be available.

The oxygen gauges should be such as to allow the gas to be bubbled through water to avoid excessive drying of the mucosae. Oxygen can be given either by the use of a tent or through a nasal catheter, depending upon the situation. In the event the latter is used, the nostrils should be alternated frequently to avoid development of a hemorrhagic rhinitis, and the catheter should be inspected frequently to detect clogging with congealed nasal mucus.

Mouth gags, tongue forceps and laryngeal mirrors are valuable aids. Saw-horses with the top bars slotted provide lifts for the foot of the bed in obtaining an adequate Trendelenburg position.

Without in any way underestimating the value of the above mentioned items, by far the greatest therapeutic factor is a nurse with "polio know-how" who is dedicated to her job. If the personnel is at all available, each respirator and bulbar case should have an experienced special nurse in constant attendance.

BIBLIOGRAPHY

1. Bodian, D.: Poliomyelitis, neuropathological observations in relation to motor symptoms, J. A. M. A. 134: 1148, 1947.
2. McCarter, J. C.: The brain stem in acute poliomyelitis, Quart. Bull., Northwestern Univ. M. School 22: 264, 1948.
3. Best, C. H., and Taylor, N. B.: Physiological basis of medical practice, ed. 4, 1945, Williams & Wilkins Co., Baltimore.
4. Hart, V. K.: Personal communication.
5. Saphir, O.: Visceral lesions in poliomyelitis, Am. J. Path. 21: 99, 1945.

HYPOPITUITARISM: STUDIES IN PITUITARY TUMORS AND SIMMONDS' DISEASE [*]

By K. E. Paschkis and A. Cantarow, *Philadelphia, Pennsylvania*

The hypophysectomized animal has proved to be the most valuable preparation in the study of pituitary physiology. Patients with destructive lesions of the anterior pituitary offer an opportunity for similar investigations of the physiology of the human pituitary gland. The studies reported in this paper were undertaken because relatively few such investigations have been published.

MATERIAL AND METHODS

The 17 patients studied include cases of pituitary or parapituitary tumors (chromophobe adenomas, craniopharyngiomas) and nontumor cases (table 1). In addition to clinical examination and routine laboratory tests, the following studies were made: basal metabolic rate, serum cholesterol, insulin

TABLE I

Tumor cases:

Chromophobe adenoma, verified by operation	8
Chromophobe adenoma, no operation	3
Craniopharyngioma, verified by operation	2
Cyst, probably craniopharyngioma, operation	1

Nontumor cases:

"Simmonds' disease," postpartum, diagnosed clinically	2
Fibrosis of the pituitary, verified by autopsy—cause undetermined	1
	17

tolerance test,[8] salt deprivation test (Cutler, Power and Wilder [1]), urinary 17-ketosteroids,[10] urinary gonadotropins,[8] roentgenograms of the skull, and examination of fundi and visual fields.

RESULTS AND DISCUSSION

The pertinent data are tabulated in table 2. The manifold physiologic actions of the anterior pituitary are due to elaboration of six hormones which have been isolated from the gland, viz.: growth, follicle-stimulating, luteinizing, lactogenic (luteotropic), adrenocorticotropic, and thyrotropic hormones. The existence of other anterior pituitary hormones has been claimed but not substantiated. In the present study an attempt was made

to investigate, directly or indirectly, the adequacy of secretion of each of these, with the exception of the growth and lactogenic hormones.

Thyrotropic Hormone. A suitable assay procedure for thyrotropic hormone has been developed recently [2] but was not available when the data presented here were being accumulated. Thyrotropic function was evaluated by determining thyroid function, on the basis of clinical symptoms and basal metabolic rate. Whereas hypometabolism may be due to causes other than thyroid or pituitary-thyroid deficiency, the low basal metabolic readings in these cases were tentatively interpreted as indicating thyrotropic-thyroid deficiency. Arbitrarily, basal metabolic values of -25 per cent or lower were considered significant, because such low readings, although occurring in other types of "hypometabolism," are unusual in the absence of thyroid deficiency except in cases of advanced starvation. Eight cases had basal metabolic values between -26 and -50 per cent. These included the two women with postpartum panhypopituitarism (Simmonds' disease). Five of the eight presented in varying degree clinical manifestations of hypothyroidism such as dryness of skin and hair, drowsiness, and slowing of mental processes. Such manifestations are difficult to interpret in the presence of other pituitary deficiencies and, in six of the eight, of an intracranial tumor. In no instance was there a significant elevation of serum cholesterol. This is in keeping with experimental observations that hypothyroidism following hypophysectomy is not accompanied by elevation of serum cholesterol, and that the usual post-thyroidectomy elevation of the latter is abolished by subsequent hypophysectomy.[16] This has been attributed to inadequate food intake on the part of the hypophysectomized animal rather than to any specific influence of the anterior pituitary upon cholesterol metabolism.[8]

Adrenocorticotropic Hormone (ACTH). Assays of ACTH in serum and urine have been attempted, but no method has yet been developed of sufficient sensitivity and reproducibility to permit its use in studies of clinical hypopituitarism. The status of adrenocorticotropin secretion was therefore evaluated by studies of adrenocortical functions.

Adequacy of salt hormone secretion (11-desoxycorticosterone type of action) was tested by the procedure of Cutler et al.[1] A significantly high salt excretion indicated salt hormone failure in seven cases, which included the three cases of nontumorous panhypopituitarism. In one case (case 12) the test had to be discontinued because a crisis ("Addisonian" crisis) was precipitated. Stephens [13] has reported deficiency in salt retention in two cases of panhypopituitarism. It has been claimed that in the rat, salt hormone secretion is independent of pituitary adrenocorticotropic control.[4] The salt hormone deficiency in human panhypopituitarism reported here, as well as the occurrence of sodium and chloride retention following administration of ACTH to humans,[7] clearly demonstrates that in the human, salt hormone secretion is under pituitary control. It is well known that patients with panhypopituitarism rarely develop "Addisonian" crisis except under extreme

TABLE II

Case No. Sex Age	Diag.	Confirm.	Presenting Symptoms	Duration	BMR	Ser. Chol. Mg.%	Bl. Pr.	Cutler Test Mg.% Cl.	"Insulin Tolerance"	17-Ketost. Mg. Equiv. Androst./24 hr.	Genitalia	Urinary Gonado- tro IU/24 hr.
1 Ch. Sch. M. 51	Chromoph. Ad.	Op.	Vision Anemia	6-8 yr.	-38	175	100/65	231	Decreased	1.1	Atrophic	>96
2 Ch. G. M. 58	Chromoph. Ad.	Op.	Vision Headache	1 yr.	-27	266	130/70	104	Normal	6.3	Impotence Gynecomast.	< 6
3 G. O. M. 49	Chromoph. Ad.	Op.	Vision	½ yr.	-19	179	100/60	21	Decreased	3.6	Impotence	
4 R. S. M. 14	Cranio- pharyng.	Op.	Vision Headache	6 wks.	-34	132	100/60	67 254	Decreased	1.9	Immature	
5 T. L. F. 49	Chromoph. Ad.	O.	Vision Headache	2½ yr.	+ 4 -12	155	170/70	33 38	Normal decr. after x-ray	8.0		>96
6 E. H. F. 52	Chromoph. Ad.	O.	Vision	3 mo.	-16	190	130/90	54	Decreased	9.7	Menopause	>96
7 S. S. F. 52	Chromoph. Ad.	Op.	Vision Headache	6 mo.	-14	175	120/80	7	Normal	7.3	Menopause	27 < 6 (After op.)
8 E. A. F. 23	Cranio- pharyng.	Op.	Vision Headache	7 yr.	-27	193		33	Normal	1.4	Menstruating Child, age 2	33
9 K. P. F. 35	Chromoph. Ad.	Op.	Vision Headache Weakness	2 yr.	-26	222	130/70	69	Normal	2.0	Amenorrhea ½ yr. 2 chil- dren, 15, 10	< 6

TABLE II—*Continued*

Case No. Sex Age	Diag.	Confirm.	Presenting Symptoms	Duration	BMR	Ser. Chol. Mg.%	Bl. Pr.	Cutler Test Mg.% Cl.	"Insulin Tolerance"	17-Ketost. Mg. Equiv. Androst./24 hr.	Genitalia	Urinary Gonado-trop. IU/24 hr.
10 G. K. M. 44	Chromoph. Ad.	Op.	Vision Headache	1½ yr.	−17	167		291	Normal	3.0	Impotence	<6
11 G. M. F. 40	Chromoph. Ad.	O.	Vision	14 yr.	−10	201	200/120	156	Decreased	2.6	Surg. menop.	>192
12 J. G. M. 56	Chromoph. Ad.	O.	Vision Weakness	3 yr. 1 yr.	−9	296	90/60	Crisis		1.8	Impotence	<6
13 G. E. M. 26	Cyst	Op.	Headache Vision	5 yr. 1 yr.	−15	193	110/70	48	Normal	4.7	Decr. libid. and potency	<6
14 M. K. F. 49	Chromoph. Ad.	Op.	Vision Weakness Headache	1½ yr. 7 mo. 3 mo.	−31	270	120/70	63	Normal	8.4	Amenorrhea 3 yrs.	<6
15 E. S. F. 45	Simmonds'		Weakness Fainting	12 yr.	−50	187	90/60	334	Decr., coma	0.8	Atrophy Amenorrhea	<6
16 Wm. S. M. 57	Simmonds'	Aut.	Weakness	10 yr.	−14	231	80/55	461	Almost normal	0.8	Impotence Atrophy	<6
17 S. Da. F. 32	Simmonds'		Weakness	2½ yr.	−30	205	90/50	341	Decreased	0.2	Amenorrhea	<6

provocation, such as deliberate withdrawal of dietary sodium chloride with simultaneous administration of potassium, which forms the basis of the test procedure of Cutler et al. (case 12). This is in striking contrast to the frequent occurrence of hypoglycemic episodes in such patients, resulting largely, but not exclusively, from loss of "sugar hormone" secretion by the adrenal cortex.

Adequacy of sugar hormone elaboration may be investigated in several ways. C-11 oxygenated steroids are excreted in the urine; the amounts excreted may be determined by chemical methods,[3, 9, 15] and those with biologic activity may be assayed.[18] Inasmuch as these procedures were applied in only a few of the cases in this series, the results are not included in this report. The same applies to the blood eosinophil response to epinephrine and to ACTH.[7, 17]

The status with regard to C-11 oxygenated compounds was evaluated by the response to either insulin or, in some instances, to intravenously administered glucose. Insulin-induced hypoglycemia stimulates the anterior pituitary to secrete ACTH, which in turn causes increased secretion of the adrenocortical C-11-oxygenated compounds ("sugar hormones"). In the absence of either pituitary or adrenocortical function there is inadequate restoration of the pre-injection blood sugar level. Following intravenous infusion of glucose, the hyperglycemia causes increased secretion of insulin which, if not opposed by adrenocortical sugar hormone, results in a prolonged subsequent period of hypoglycemia. Whereas both procedures ultimately test adrenocortical responsiveness to the effects of insulin, the insulin test is much the more sensitive, probably chiefly because there is no "covering" exogenous glucose, and also perhaps because hypoglycemia is developed more suddenly.

Seven patients, five of whom were tumor cases, showed marked "hypoglycemia irresponsiveness." Hypoglycemic coma was precipitated in one (case 15) of the three without tumor. One patient (case 5), a case of tumor not verified by operation and diagnosed on clinical grounds as chromophobe adenoma, had a normal response to insulin but exhibited hypoglycemia irresponsiveness after roentgen irradiation of the pituitary.

The status of "N-hormones" (protein-anabolic) was gauged by the levels of urinary 17-ketosteroids. Four of the nine women in this series had excretion levels of less than 2 mg. equivalents of androsterone per 24 hours; one excreted less than 3 mg. and four more than 3 mg. Of the eight men, five excreted less than 3 mg., one between 3 and 4 mg., and four more than 4 mg. per 24 hours.

Evidence of panhypocorticalism was obtained in two cases (cases 15 and 17). However, in others there was a conspicuous dissociation of the findings in the three broad spheres of adrenocortical activity. For example, in cases 10 and 16, abnormal salt excretion was found in the presence of a normal response to insulin. Normal 17-ketosteroid excretion in the presence of impaired response to insulin-induced hypoglycemia was observed

in case 6. Conversely, low 17-ketosteroid excretion occurred in cases showing a normal response to insulin (cases 8, 9, 10 and 16).

There is at present some controversy regarding the nature and identity of the "N-hormone" of the adrenal cortex and the source of urinary 17-ketosteroids of adrenal origin. Three 17-ketosteroids with androgenic activity have been isolated from the adrenal cortex, but these compounds do not appear in the urine. 17-ketosteroids with an origin in the "sugar hormone" type of compound, suggested by the presence of oxygen at C–11, have been isolated, and the production by the adrenal cortex of androgenic N-hormones, independent of the C–11 oxygenated sugar hormones, has been questioned. The observed dissociation of "sugar hormone deficiency" and "N-hormone deficiency" as reflected in 17-ketosteroid excretion adds to the bulk of evidence for adrenal production of N-hormones. We are of course aware that clinical observations of the type reported cannot constitute conclusive evidence in this connection.

Gonadotropic Hormones. Gonadotropic function was evaluated by the clinical condition of the genitalia, functional and anatomic, and by assay of urinary gonadotropins.

In the female group, one woman, aged 23 (case 8: craniopharyngioma), was menstruating fairly regularly, had given birth to a child two years previously, still had some secretion from her breasts, and prolactin was demonstrable in the urine. Her urinary gonadotropin excretion was 33 IU per 24 hours. In contrast to the normal gonadotropin excretion and perhaps abnormally prolonged prolactin secretion, her 17-ketosteroid excretion was 1.4 mg. per 24 hours and her basal metabolic rate — 27 per cent, suggesting some degree of adrenocorticotropic and thyrotropic inadequacy. It is noteworthy that her adrenal failure was far from complete, both insulin response and salt excretion being normal. Three menopausal women (cases 5, 6 and 11, aged 49, 52 and 40 years, respectively) had high urinary gonadotropin levels of more than 92 IU per 24 hours, indicating a normal pituitary response to cessation of ovarian function. Two of these (cases 5 and 6) exhibited no functional manifestations of hypopituitarism, whereas one (case 11) showed low 17-ketosteroid excretion and hypoglycemia irresponsiveness, indicating partial adrenocorticotropic failure. The two women with panhypopituitarism of Simmonds' type were amenorrheal, with atrophic genitalia and urinary gonadotropins of less than 6 IU per 24 hours.

All of the males complained of loss of potency. There was marked atrophy of the genitalia in two cases (cases 1 and 16). The urinary gonadotropins were less than 6 IU per 24 hours in all but one (case 2); however, many normal men do not excrete more than 6 IU, and inasmuch as no attempt was made to assay at lower levels, these findings cannot be interpreted as deficient gonadotropin excretion. Case 2 is of some interest, his gonadotropin excretion being in the castrate range (more than 96 IU). Evidently his gonadal failure was not the result of hypopituitarism, but represented

rather a condition of primary hypogonadism, fortuitously associated with a pituitary tumor.

The overall picture of functional impairment by nonfunctioning pituitary or parapituitary tumors (chromophobe adenoma, craniopharyngioma, etc.) is kaleidoscopic. One extreme is represented by cases with no evidence of functional deficiencies (cases 5 and 7); the other extreme is exemplified by cases of panhypopituitarism, with failure of thyrotropic, adrenocorticotropic and gonadotropic secretion (cases 1 and 4). Between these two extremes are cases which give indications of certain deficiencies, whereas other functions appear to be unimpaired. The most baffling picture is presented by cases in which there is a dissociation of adrenal functions, only one or two of which are impaired. A similar dissociation is also observed in primary Addison's disease. In the latter, destruction of the adrenal cortex might conceivably spare areas of elaboration of certain hormones; however, such dissociation in hypopituitarism, in which condition there is atrophy of the adrenal cortex, suggests that under circumstances not as yet understood, production of certain types of compound by the adrenal might be maintained at the expense of others. An alternate explanation would be the assumption of the existence of more than one adrenocorticotropic hormone, for which assumption there is no adequate evidence.

It is noteworthy that the mechanical damage produced by a pituitary tumor may be quite as extensive, as judged by bony changes in the sella turcica and by impairment of visual fields, in cases in which pituitary function is practically intact as in those with panhypopituitarism. The presence or absence of hypopituitarism in cases of tumor probably depends on the amount of functioning, nontumorous anterior pituitary tissue which escapes destruction by pressure. The limiting factor may well be the structure of the diaphragm of the sella, and the consequent resistance it offers to early upward growth of the tumor. Wide variations are known to occur in this structure.[11] The fact that secretion of one or other of the pituitary hormones may continue in the face of deficiency in others is more difficult to explain. Only a large number of histologic studies, including differential cell counts, of the nontumorous portion of the anterior pituitary might perhaps elucidate such cases, if adequate functional studies had been secured before autopsy. Such information is completely lacking.

The two women with "Simmonds' disease" (cases 15 and 17) gave a typical history of severe postpartum shock and presented a characteristic picture of panhypopituitarism.[12]

The one man (case 16) also presented a typical picture of panhypopituitarism, with the exception of a normal response to insulin. In this case, autopsy revealed extensive but not complete fibrosis of the anterior pituitary. No cause could be elicited on the basis of either the history or the autopsy findings. This case will be reported in detail elsewhere.

The studies reported in this paper were undertaken as an investigation of human pituitary physiology, with no immediate practical or therapeutic

purpose. The fact that metabolic deficiencies are present in many of the tumor cases is, however, of importance to the surgeon. The adrenocortical deficiencies are particularly important. Only in exceptional cases will they be manifest, or even suspected, upon routine clinical examination. Since the subclinical deficiencies demonstrable only by specific tests suggest the presence of adrenocortical borderline adequacy without reserve, such patients may be expected to tolerate operation poorly unless they receive adequate supportive treatment preoperatively and postoperatively. Appropriate tests should, therefore, be performed routinely before operation.

SUMMARY AND CONCLUSIONS

1. Studies are reported on 14 cases of pituitary and parapituitary tumors (chromophobe adenomas, craniopharyngiomas) and three cases of "non-tumorous" panhypopituitarism.

2. The degree of impairment of anterior pituitary function by the tumors varies from none to severe panhypopituitarism. The degree of impairment is entirely unrelated to the extent of mechanical-neurologic damage produced by the tumor. It is suggested that the structure and resistance of the diaphragm of the sella may be a decisive factor, some tumors readily overcoming the resistance of the diaphragm and growing upward before producing extensive compression of the nontumorous remnant of the anterior pituitary.

3. Secretion of the various pituitary hormones is not necessarily impaired to the same degree; this leads to various combinations of hypothyroid, hypoadrenocortical and hypogonadal manifestations. Even the individual functions of the adrenal cortex, attributable to different types of adrenocortical steroids, are not always all impaired in the same individual, nor to the same degree.

4. The occurrence of salt-hormone deficiency of the adrenal cortex in hypopituitarism adds to the evidence that, in humans, the secretion of salt-hormone (11-desoxycorticosterone) is under pituitary adrenocorticotropic control.

5. Whereas this study was undertaken as a physiologic investigation of the human pituitary, the frequency of occurrence of subclinical deficiencies, especially of the adrenal cortex, found in patients with pituitary tumor warrants attention by the surgeon. Routine performance of appropriate tests, followed by supportive preoperative and postoperative treatment with adrenocortical hormone, is suggested in cases showing evidence of such deficiencies.

BIBLIOGRAPHY

1. Cutler, H. H., Power, M. H., and Wilder, R. M.: Concentrations of chloride, sodium and potassium in urine and blood. Their diagnostic significance in adrenal insufficiency, J. A. M. A. 111: 117–122, 1938.
2. D'Angelo, S. A., and Gordon, A. S.: The simultaneous detection of thyroid and thyrotropic hormone in vertebrate sera, Endocrinology 46: 39, 1950.

3. Daughday, W. H., Jaffe, H., and Williams, R. H.: Chemical assay for "cortin," J. Clin. Endocrinol. **8**: 166, 1948.

4. Deane, H. W., and Greep, R. O.: A morphological and histochemical study of the rat's adrenal cortex after hypophysectomy with comments on the liver, Am. J. Anat. **79**: 117-146, 1946.

5. Enteman, C., Chaikoff, J. L., and Reichert, F. L.: Blood lipids of the hypophysectomized thyroidectomized dog, Endocrinology **30**: 794, 1942.

6. Fluhman, C. F.: Menstrual disorders, 1939, W. B. Saunders Co., Philadelphia.

7. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G.: Clinical studies with pituitary adrenocorticotropin, J. Clin. Endocrinol. **8**: 15, 1948.

8. Fraser, R., and Smith, P. H.: Simmonds' disease or panhypopituitarism (anterior), Quart. J. Med. n.s. **10**: 297–330, 1941.

9. Heard, R. D. H., and Sobel, H.: A colorimetric method for the estimation of reducing steroids, J. Biol. Chem. **165**: 687, 1946.

10. Holtorff, A. F., and Koch, F. C.: The colorimetric estimation of 17-ketosteroids and their application to urine extracts, J. Biol. Chem. **135**: 377, 1940.

11. Schaeffer, J. P.: Some points in the regional anatomy of the optic pathway, with special reference to tumors of the hypophysis cerebri and resulting ocular changes, Anat. Rec. 28: 243, 1924.

12. Sheehan, H. L., and Summers, V. K.: The syndrome of hypopituitarism, Quart. J. Med. n.s. **18**: 319, 1949.

13. Stephens, D. J.: Pituitary and adrenocortical insufficiency, J. Clin. Endocrinol. **1**: 109, 1941.

14. Swann, H. G.: The pituitary-adrenocortical relationship, Physiol. Rev. **20**: 493–521, 1940.

15. Talbot, N. B., Saltzman, A. H., Wixom, R. L., and Wolfe, J. K.: The colorimetric assay of urinary corticosteroid-like substances, J. Biol. Chem. **160**: 535, 1945.

16. Thompson, K. W., and Long, C. N. H.: The effect of hypophysectomy upon hypercholesterolemia of dogs, Endocrinology **28**: 715, 1941.

17. Thorn, G. W., and Forsham, P. H.: Metabolic changes in man following adrenal and pituitary hormone administration, Recent Progress in Hormone Res., Vol. 4, 1949, Academic Press, New York.

18. Venning, E. H., Kazmin, V. E., and Bell, J. C.: Biological assay of adrenal corticoids, Endocrinology **38**: 79, 1946.

DIABETES AND PREGNANCY: WITH SPECIAL REFERENCE TO THE PREDIABETIC STATE *

By James M. Moss, M.D., *Washington, D. C.*, and H. B. Mulholland, M.D., F.A.C.P., *Charlottesville, Virginia*

Pregnancy and Diabetes

For many years it has been realized that pregnancies in diabetic women are associated with complications which lead to a high fetal mortality rate.[1] The most important abnormalities are intrauterine death of the fetus, neonatal deaths and spontaneous abortion. Of lesser significance are large size of the fetus, preëclamptic toxemia, prematurity, breech presentation, polyhydramnios, uterine inertia, and an increased incidence of congenital defects. Because of these abnormalities, the fetal mortality rate varies from 30 to 60 per cent. The larger figure is obtained if the spontaneous abortions of early pregnancy are included; the smaller figure is obtained if only the last month is included. Before the advent of insulin, the maternal mortality rate in diabetic mothers was 25 per cent [1] to 30 per cent,[2] but now this is negligible. The fetal mortality rate, on the other hand, has remained high in spite of insulin and good diabetic control. That these same complications occur many years before the clinical diagnosis of diabetes is made was recognized in 1928 by Bowcock and Greene,[3] in 1933 by Skipper,[4] and in 1935 by White.[5] The most intensive studies of this phase of the question have been by Miller [6, 7, 8, 9] and his associates. Herzstein and Dolger,[10, 11] however, have taken exception to his findings and report no increased fetal mortality in the prediabetic years.

This study was undertaken in order to determine the fetal mortality rate and the incidence of complications in a series of diabetic patients before and after the diagnosis of diabetes has been established. The authors were also interested in evaluating measures which might be used to reduce the mortality rate. Similar studies have recently been reported by Patterson and Burnstein,[12] Barns and Morgans,[13] and Gilbert.[14]

Methods and Materials

The pregnancy records of 500 diabetic women seen in the University of Virginia Hospital in the past 20 years were reviewed. The data on the charts of 72 patients were sufficiently detailed to be used in the study. In the remainder of these cases either the women had never been pregnant or else the data were too incomplete to be used. In many cases the accuracy of the data was verified by personal interview with the patient or review of the chart of the offspring. Because of the fact that abnormal findings

are more apt to be recorded than are normal findings, it is possible that some of the figures are weighted to show an increased incidence of abnormalities. Our figures show a close correlation with those obtained by other authors using different methods of study.   Of the 72 patients, all were clinic patients except for one private patient.   Twenty-seven of them were Negroes. Thirty (42.2 per cent) were definitely obese at the onset of pregnancy. Seventeen (24 per cent) of our patients had a family history of diabetes, which compares with 17.8 per cent as reported by Herrick and Tillman.[15] Twenty-eight of these patients (39 per cent) developed diabetes before the age of 35 years; the remainder developed diabetes after 35.   The family history was positive in 29.6 per cent of the younger group and in 20.4 per cent of the older group.   The average age at the time of the diagnosis of diabetes in the entire series was 38 years.   This compares with the age of 45.7 years reported by Herzstein and Dolger,[11] 47.1 years reported by Kriss and Futcher,[16] and 48 years reported by Paton.[17]   The above authors included only women with pregnancies before the onset of diabetes.   We included those with pregnancies both before and after the diagnosis of diabetes.

RESULTS

Fertility: There were 450 pregnancies in the group of 72 women, with an average of 6.25 pregnancies per patient.   This is a larger number of pregnancies per patient than has been previously reported, but perhaps can be explained by the high incidence of large families in the rural area from which most of the patients came.   Patterson and Burnstein [12] found no evidence of decreased fertility in their patients before the onset of clinical diabetes.   Paton [17] reports that 7.3 per cent of his married diabetic patients did not become pregnant.   The incidence of sterile marriages in the non-diabetic is reported to be 10 per cent.[18]   Thus it would seem that fertility is no problem in the prediabetic * or in the diabetic patient today, although apparently it was a problem in diabetic women before the days of insulin.[1, 2, 15]

Spontaneous Abortion: Because of the difficulty in verification of the diagnosis of spontaneous abortion, it is doubtful if statistical significance can be attached to any figures for that complication.   In 444 pregnancies, the rate was found to be 12.2 per cent before the clinical diagnosis of diabetes and 21.4 per cent after this diagnosis was made.   It is important to notice that the highest incidence of abortions was in the group found to have diabetes during the pregnancy and whose diabetes was in a poor state of control.   Eastman [2] reported that the spontaneous abortion rate in the non-diabetic is 10 per cent; in the controlled diabetic, 16 per cent, and in the uncontrolled diabetic, 25 per cent.   Barns and Morgans [13] found the rate to be 14 per cent in the diabetic, 13.3 per cent in the prediabetic, and 11.8

---

* By the term "prediabetic," we mean those patients who do not have clinical diabetes but who later develop it.

per cent in the nondiabetic.   Mengert and Laughlin [19] reported the rate to be 26.2 per cent in the diabetic and 17.9 per cent in the prediabetic.

We cannot agree with Patterson and Burnstein,[12] who state that diabetes has no effect on the incidence of spontaneous abortions.   Our figures indicate, however, that the effect is small and that it is possibly related to the occurrence of acidosis.

Stillbirths: The birth of a large macerated fetus at term is the most striking complication of pregnancy in the diabetic.   In our series, 26.2 per cent of the pregnancies in the diabetic and 8.5 per cent in the prediabetic group ended in stillbirth.   In the five years preceding the onset of diabetes, the rate was 16.7 per cent.   This rate gradually declined to 1.8 per cent 26 years before the diagnosis of diabetes.   The incidence of stillbirths in all deliveries is 2.14 per cent, according to Stander.[20]   Mengert and Laughlin [19] report

<div align="center">

TABLE I

Fetal Mortality in Diabetic and Prediabetic Pregnancies

</div>

	Number Pregs.	Average Age	Living Babies		Spontaneous Abortions		Stillbirths		Neonatal Deaths	
			No.	%	No.	%	No.	%	No.	%
Total diabetics	42	31.9	19	45.3	9	21.4	11	26.2	3	7.1
Diagnosis during pregnancy	18	32.4	6	33.3	5	27.8	6	33.3	1	5.6
Diagnosis before pregnancy	24	31.5	13	54.1	4	16.7	5	20.8	2	8.3
Total prediabetic	402	28.2	292	76.2	49	12.2	34	8.5	27	6.7
1–5 years before	54	30.3	33	61.1	11	20.4	9	16.7	1	1.8
6–10	78	31.4	52	66.7	12	15.3	8	10.3	6	7.7
11–15	73	29.5	52	71.3	11	15.1	5	6.8	5	6.8
16–20	83	27.1	67	80.8	3	3.6	8	9.6	5	6.0
21–25	59	26.4	46	78.0	3	5.1	3	5.1	7	11.8
26–40	55	23.2	42	76.3	9	16.4	1	1.8	3	5.5
Treated diabetics	6	35.4	6	100.0	0	0	0	0	0	0

a rate of 17.8 per cent in diabetics and of 11.9 per cent in prediabetics. Eastman [2] and Englehardt and Melvin [21] report rates of 25 per cent and 21.5 per cent, respectively, in diabetic pregnancies.   It has been demonstrated that this rate is not appreciably affected by the accuracy of the diabetic control.[1]   In order to prevent this high stillbirth rate, several authors [1, 22, 23, 24, 25, 26] have recommended the routine performance of a Cesarean section in the thirty-seventh week of pregnancy.   An equal number of authorities think that routine Cesarean section is unjustified.[12, 15, 19, 27, 28]   We agree with the latter group.   There were three sections (7.1 per cent) in the 42 diabetic pregnancies and one section (0.2 per cent) in the 402 prediabetic pregnancies.   All of these operations were done for obstetrical reasons.

Neonatal Deaths: The children born to diabetic mothers tend to be large, fat, edematous and rather sluggish.   Cyanosis and dyspnea are manifesta-

tions of the high incidence of atelectasis.   At autopsy these babies are found
to have cardiac hypertrophy, hepatomegaly, extramedullary erythropoiesis,
genital hyperplasia, adrenal hyperplasia, and eosinophilia of the anterior
lobe of the pituitary gland.[29, 30]   There is a striking resemblance to the
pathologic findings in erythroblastosis fetalis.[31]   At one time, hypogly-
cemia was thought to be the cause of death in infants born to diabetic moth-
ers, but this is probably of very little significance.[31, 32]

The incidence of neonatal deaths in our diabetic patients was 7.1 per cent.
Bill and Posey[24] report a neonatal death rate of 11.4 per cent, while East-
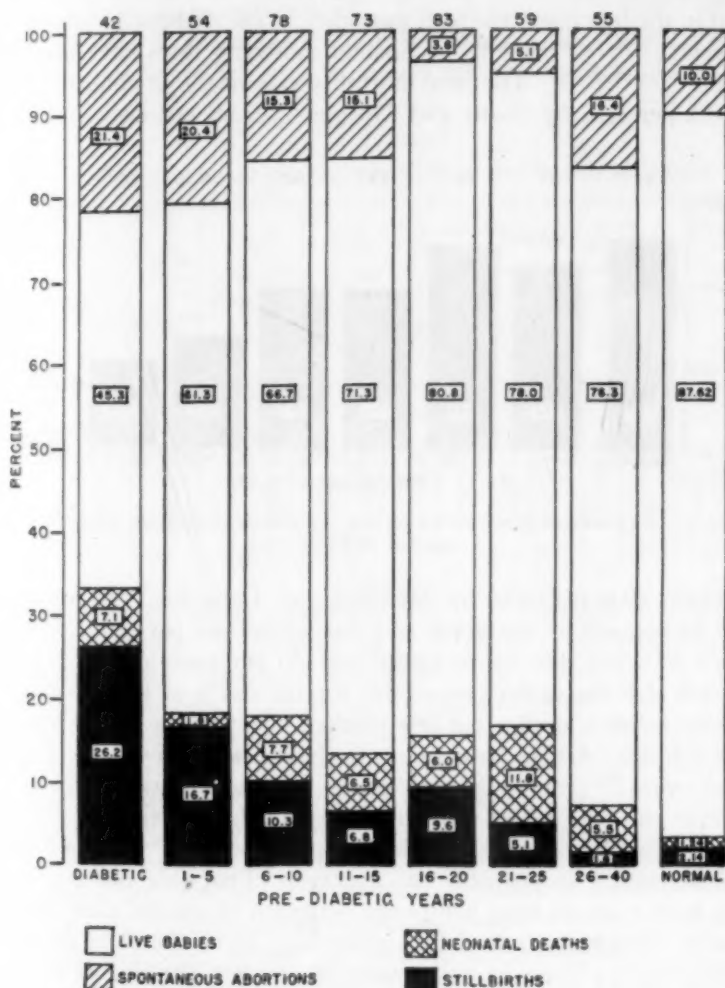man[2] reports a rate of 18 per cent in children born to mothers with diabetes.

Fig. 1. Fetal mortality rates in diabetic, prediabetic and normal pregnancies. The numbers
at the top of each column indicate the number of patients in each group.

The latter author states that 43 per cent of the infants were moribund during the first few days.   The expected neonatal death rate after all deliveries is 1.24 per cent.[20]   In our prediabetic group the neonatal death rate was 6.7 per cent.   The neonatal mortality in our patients was higher in those delivered at home than in those delivered in the hospital.   This mortality probably can be reduced by careful pediatric care, which includes postural drainage, dehydration, oxygen and mechanical stimulation if necessary.[22]

Total Fetal Mortality Rate: Our overall fetal mortality rate, including abortions, stillbirths and neonatal deaths, was 54.7 per cent in the diabetics and 27.4 per cent in the prediabetics; in the five years immediately preceding the diagnosis of diabetes, it was 38.9 per cent.   In most of the large series reported in the literature, the fetal mortality in the diabetic is between 40 and 60 per cent.[1, 2, 13, 21, 29, 33, 34, 35, 36]   Smaller mortality rates have been reported by some.[7, 23, 24, 25, 37, 38]   The fetal mortality rate in the prediabetic was found to be 20.5 per cent by Barns and Morgans,[13] 23.8 per cent by Dolger and
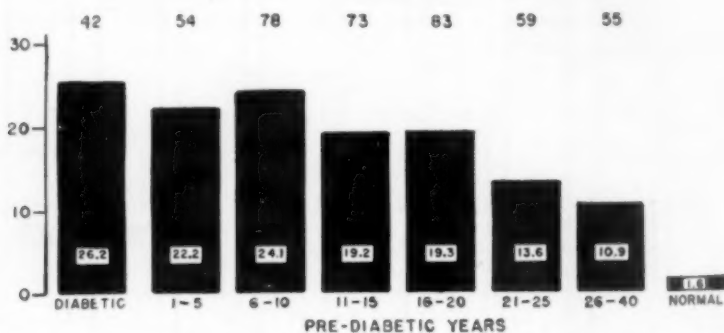

FIG. 2.   Incidence of babies weighing over 10 pounds in diabetic, prediabetic and normal pregnancies.

Herzstein,[10] 29.8 per cent by Mengert and Laughlin,[19] 19.8 per cent by Miller,[9] 23 per cent by Patterson and Burnstein,[12] 27 per cent by Palmer and Barnes,[39] 39.3 per cent by Skipper,[4] and 20 per cent by White.[5]   Thus it is apparent that the factor responsible for the death of the offspring of diabetic women has a similar but less marked effect in the prediabetic woman.

Large Babies: Of the babies born to these diabetic mothers, 26.2 per cent weighed over 10 pounds (4,500 gm.).   In the prediabetic patients, 19.8 per cent of the 339 babies were over 10 pounds in weight.   The expected incidence of babies over 10 pounds is 1 per cent [22, 40, 41, 42] to 4.5 per cent,[16] but 1.5 per cent [43] is probably the average.   That this increased incidence of large babies occurs long before the detection of clinical diabetes is shown in table 2.   Others have found a similar high incidence of large babies.[1, 2, 7, 12, 16, 22, 24, 25, 28, 37]   There is no correlation between the size of the baby and (a) the control of the diabetes,[1, 2, 29] (b) the weight of the mother,[5, 42, 33] (c) the incidence of toxemia,[22, 28] or (d) the age of the mother.[26]   The mortality

rate in the large babies born to diabetics and prediabetics is no higher than that of large babies born to nondiabetics, but the mortality rate of large babies in general is about three times higher than that for normal sized babies.[40] Thus it is likely that many apparently normal mothers of large babies are actually in the prediabetic state. Kriss and Futcher [16] have shown that 58 per cent of diabetic women will have one or more large babies at an average interval of 24.2 years before their diabetes is diagnosed. They have constructed tables to show the accuracy with which one can predict the onset of diabetes in a woman with a large child. Our figures would tend to support this view. It should be noted that the percentage of large babies progressively decreases as the interval between the pregnancy and the diagnosis of diabetes increases. Part of this is due to the fact that any weight which was not known was called normal, and there were more unknown weights in the pregnancies which occurred earlier.

TABLE II

Complications of Pregnancy in Diabetic and Prediabetic Women

	Number Pregs.	Normal Pregs.		Large Babies		Premature Delivery		Toxemia		Polyhydramnios		Breech Present.		Cesarean Section	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total diabetic	42	6	14.3	11	26.3	6	14.3	18	42.8	4	9.5	3	7.1	3	7.1
Diagnosis during pregnancy	18	1	5.6	5	27.8	2	11.1	12	66.7	1	5.6	2	11.1	2	11.1
Diagnosis before pregnancy	24	5	20.8	6	25.0	4	16.7	6	25.0	5	20.8	1	4.7	1	14.7
Total prediabetic	402	168	42.0	79	19.8	27	6.7	57	14.2	5	1.2	17	4.2	1	0.2
1–5 years before	54	14	25.9	12	22.2	2	3.7	14	25.9	3	5.5	1	1.8	0	0
6–10	78	18	24.1	18	24.1	6	7.7	15	19.2	4	5.1	2	2.6	0	0
11–15	73	31	42.5	14	19.2	5	6.8	11	15.1	0	0	2	2.7	1	1.4
16–20	83	45	54.2	16	19.3	3	3.6	11	13.2	0	0	6	7.2	0	0
21–25	54	33	56.0	8	13.6	5	8.5	3	5.1	0	0	3	5.1	0	0
26–40	55	26	47.2	6	10.9	4	7.8	3	5.5	0	0	3	5.5	0	0

Premature Deliveries: Premature delivery occurred in 14.3 per cent of our diabetics and 6.7 per cent of the prediabetics. Lavietes, Leary, Winkler and Peters [28] and Englehardt and Melvin [21] report an incidence of 9.7 per cent and 4.3 per cent, respectively, in diabetic pregnancies. The expected incidence, according to Stander,[44] is 2.7 per cent. It is doubtful if prematurity has much effect on the fetal mortality rate in diabetic pregnancies, as some authors [1, 2, 24, 39] recommend the induction of premature labor in an effort to decrease fetal mortality.

Polyhydramnios: The incidence of polyhydramnios is very difficult to determine accurately, as it is usually not possible to measure the amount of amniotic fluid. In our patients, polyhydramnios occurred in 9.5 per cent of the diabetics and in 1.2 per cent of the prediabetics. Other authors report an incidence ranging from 2.3 per cent [24] to 24 per cent,[27] with an average of 10 per cent.[2, 19, 28, 40] The expected incidence is 0.4 per cent.[45]

Polyhydramnios is apparently more common in patients with hyperglycemia than in those who are well controlled.

Breech Presentation: The figures on this are probably not complete, as the method of presentation was not always recorded. We found an incidence of 7.1 per cent in diabetics and 4.2 per cent in prediabetics. The expected rate in all deliveries is 3 to 4 per cent.[46] White [32] reports the amazing figure of 33 per cent. Patterson and Burnstein [12] report the more conservative figure of 11.5 per cent. The increased incidence of breech presentation is thought to be due to the large size of the fetus.
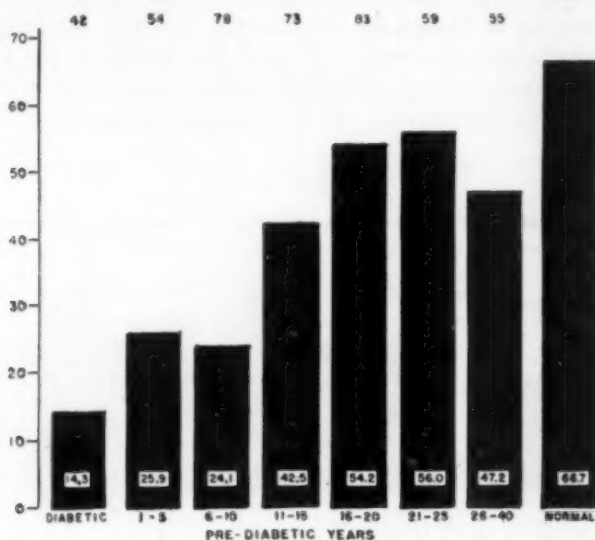

Fig. 3. Incidence of uncomplicated pregnancies in diabetic, prediabetic and normal women.

Toxemia: Evidence of toxemia was found in 42.8 per cent of the diabetics and in 14.2 per cent of the prediabetics. This latter rate probably would be higher if more detailed information were available on the prediabetic group. In nondiabetics the incidence of toxemia is about 7 per cent.[2] In diabetics the incidence of toxemia varies from 24 per cent [19] to 70 per cent,[22] with an average of 36 per cent [1] to 39 per cent.[28] Allen [22] has shown that the incidence of toxemia is greatly increased by obesity and age. Transient "benign" glycosuria is said to be often followed by toxemia.[22] It is quite likely that the incidence of toxemia can be reduced by discouraging obesity,[33] limiting salt intake and feeding a high protein diet.

Congenital Defects: An increased incidence of congenital defects has been noted by White,[1] Barns,[27] Miller [9] and Hurwitz and Irving.[37] Like Patterson and Burnstein,[12] we have not recognized this.

Hormonal Treatment: We have treated six proved diabetics with large doses of estrogens and progesterone as recommended by White.[1] Because of the expense of the early treatment schedules, or because the patient was

seen first in the latter part of the pregnancy, none received the full recommended dosage. In spite of this, there were no fetal deaths in these six pregnancies. Three of the pregnancies were entirely normal. Two had a mild toxemia and one had a premature separation of a placenta previa. Perhaps if they had been treated adequately according to our present standards (table 3), the toxemia could have been prevented. None of these treated patients had large babies and none required Cesarean section. No definite conclusions can be drawn from six patients. However, review of the past histories of these patients shows that the fetal mortality rate in their 26 previous pregnancies was 27 per cent and that only 10 (38.5 per cent) of these previous pregnancies were entirely normal. These patients were followed more closely than in their previous pregnancies, but the only variation in their management was the administration of hormones.

DISCUSSION

Hormonal Aspects: In the past 15 years Smith and Smith [47, 48, 49] have shown that diabetic women who have complications of pregnancy usually have an elevated serum gonadotropin level and a decreased urinary excretion of estrogen and pregnandiol. As a general rule, the fall in urinary estrogen excretion occurs 10 weeks before and the rise in serum gonadotropin five weeks before the occurrence of the complications. These findings have been confirmed by White and Hunt,[50] Watts and Adair,[51] Jordan,[52, 53] Palmer and Barnes,[39] and Rubin, Dorfman, and Miller.[54] Priscilla White [32] has applied these results in the treatment of 300 diabetic pregnancies. She has found that approximately one-fourth of the women had normal hormonal assays, and that the fetal survival rate in this group was 97 per cent. The fetal survival rate in the group with abnormal hormonal assays was 50 to 60 per cent, and about half of the women in this group had toxemia of pregnancy. These figures are comparable to the 54.6 per cent which we observed in diabetic pregnancies. When White's patients with abnormal hormonal assays were treated with estrogens and progesterone in doses sufficiently high to correct the hormonal abnormalities, the fetal survival rate was increased to 92 per cent and the incidence of toxemia reduced to 5 per cent. Various dose schedules have been used over a period of years, and treatment was very expensive with the original schedules.[50] Subsequent studies by Smith, Smith and Hurwitz [56] have shown that diethylstilbestrol alone is as effective in correcting the hormonal abnormalities as the more expensive naturally occurring estrogens and progesterone. Also, diethylstilbestrol is equally as effective in preventing the complications of pregnancy.[32, 53, 55, 57] The dosage schedules currently recommended are shown in table 3. It now costs around $50 to treat an entire pregnancy. From our limited experience, and from an analysis of the literature, we do not hesitate to recommend this treatment for use in all diabetic pregnancies.

The Prediabetic State: Our figures indicate that the complications of pregnancy common to diabetics occur long before the clinical diagnosis of diabetes. This has been previously reported.[3, 4, 6, 7, 9, 12, 13, 15, 17, 19, 22, 28, 36,56] However, no one has yet been able to ascertain how many of these so-called prediabetic women actually have a mild subclinical diabetes. Recent diabetic surveys [59, 60] indicate that there are probably twice as many diabetics as are now diagnosed and under treatment. A latent diabetes could easily have been missed in our 72 patients. As a general rule, they had one urinalysis at the time of their first visit and another at the time of delivery. Until recently, each patient with glycosuria was checked by getting only one fasting blood sugar, and if this was normal the possibility of diabetes was ignored. The initial specimen of urine was often collected as late as six

TABLE III

Schedule for Diethylstilbestrol Therapy during Pregnancy
(after Smith, Smith and Hurwitz[56])

Week of Preg.	Daily Dose in Mg.	Number of Tablets		Week of Preg.	Daily Dose in Mg.	Number of Tablets	
		5 Mg.	25 Mg.			5 Mg.	25 Mg.
7	5	1	–	22	60	2	2
8	5	1	–	23	65	3	2
9	10	2	–	24	70	4	2
10	10	2	–	25	75	–	3
11	15	3	–	26	80	1	3
12	15	3	–	27	85	2	3
13	20	4	–	28	90	3	3
14	20	4	–	29	95	4	3
15	25	–	1	30	100	–	4
16	30	1	1	31	105	1	4
17	35	2	1	32	110	2	4
18	40	3	1	33	115	3	4
19	45	4	1	34	120	4	4
20	50	–	2	35	125	–	5
21	55	1	2	36	Stop Stilbestrol		

Total No. 5 mg. tabs., 420, Total No. 25 gm. tabs., 385.

hours after breakfast, so that it might easily have failed to reflect the post-prandial rise in blood sugar. Because of the starvation that usually occurs at the time of labor, many mild diabetics will have no glycosuria at this time. Four of these patients with transient glycosuria did not have a positive diagnosis of diabetes for several years because their fasting blood sugar levels varied between 63 and 109. Two more patients, showing transient glycosuria and normal fasting blood sugar, had a positive diagnosis made by demonstrating a diabetic type of curve after a glucose tolerance test. Two patients had no glycosuria recorded in the several urinalyses on the chart, but a glucose tolerance test was done because they had given birth to several macerated stillborn children, and it showed the fasting and other blood sugars to be elevated. Subsequently, repeated urinalysis showed that both had occasional glycosuria in the afternoon and bedtime specimens.

Allen [22] and Ewald [61] report that women with renal glycosuria have the same increased number of complications as do women with diabetes. In 12 patients with glycosuria but "normal" glucose tolerance curves, Miller, Hurwitz and Kuder [7] found the fetal mortality rate to be 32 per cent. Perhaps their criteria for the diagnosis of an abnormal glucose tolerance curve are too strict. Certainly in our series, and perhaps in many others, a diagnosis of mild or latent diabetes could have been made in many of the prediabetics had it been looked for by more frequent urinalyses and glucose tolerance tests. Since there is little if any correlation between the fetal mortality rate and the severity of diabetes,[4, 7, 12, 62, 63] it is equally as important for the mild as it is for the severe diabetics to be diagnosed and treated.

The diagnosis of mild diabetes in pregnancy is often quite difficult. The test for glycosuria as originally outlined by Benedict is so sensitive that it has been reported to give a positive test on random specimens in 39.5 per cent of nonpregnant women.[64] Since there is normally an increased amount of reducing substances in the urine during pregnancy, it is no wonder that Archer [65] found 96 per cent of pregnant women to have a positive test at some time during the pregnancy. Bray [66] recommends the addition of 0.25 c.c. of urine (instead of 0.5 c.c.) to 5.0 c.c. of Benedict's reagent. This is the test which we have adopted as standard. With this modification it is necessary to have 0.3 to 0.5 per cent rather than 0.1 per cent reducing substances present in order to get a positive reaction. The use of this modification will bring the incidence of physiologic glycosuria down to less than 5 per cent [2, 4, 20] and make a positive reaction significant. Renal glycosuria is unaffected by meals,[3, 25] but glycosuria due to diabetes is increased after meals. Therefore, if all urine specimens are collected about two hours after an adequate meal, the occurrence of glycosuria will take on added significance.

After one finds glycosuria, it is necessary to ascertain whether the blood sugar is elevated. It is well known that in the mild diabetic the blood sugar may be normal in the fasting state but elevated after a meal. The average fasting blood sugar in nonpregnant women is 94 mg./100 c.c. and in the nondiabetic pregnant woman is 83 mg./100 c.c.[2] Thus it can be seen that considerable elevation of the blood sugar is necessary for the fasting blood sugar to indicate diabetes when the usual criteria are used. If laboratory economy is essential, the most helpful time to draw a single blood sugar is two hours after a meal.

For the greatest accuracy in diagnosis, one should carry out a glucose tolerance test. There are many different methods of doing these tests and the interpretation of them depends on the one used. The most widely used is the single dose of 100 gm. of glucose, followed by a blood sugar at one hour and two hours.[66] In 81 per cent of pregnant women, the two hour specimen is over 120 because it is characteristic for the blood sugar elevation to be sustained in this condition,[67] consequently it is necessary to extend the test to the third hour.[68]

Our criteria for the diagnosis of diabetes during pregnancy on the basis

of the glucose tolerance curve are (a) fasting blood sugar above 120, (b) peak sugar at one hour above 180, (c) two hour sugar above 140, or (d) three hour sugar above 120.   It is felt that such strict criteria are necessary if one is going to diagnose and treat the "prediabetic" patients. Several reports of glucose tolerance curves done at various times during normal pregnancies have appeared in the literature.[7, 14, 15, 64, 69, 70, 71]   It has been shown that there is a decreased tolerance for glucose during the second trimester, and this is the time when diabetes tends to be aggravated. The average renal threshold for glucose falls 32 mg. per cent below the normal threshold during pregnancy because of decreased tubular reabsorption.[2, 72]

Treatment of Diabetes Complicated by Pregnancy: For the most part, we now follow the routine outlined by White.[1] If the patient is obese, she is placed on a low caloric diet; otherwise she is given 30 calories per kilogram of optimal body weight.   A high protein intake (2 gm. per kilogram) is essential in the last half of pregnancy and probably should be given the entire time.   Sufficient carbohydrate to supply 50 gm. per day to the fetus in addition to an adequate amount for the mother is prescribed.   The fat content is regulated according to the desired number of calories.   Sodium intake is restricted.   An effort is made to allow no more than a 20 pound increase in maternal weight during the entire pregnancy.

Since rapid changes in insulin requirements may occur, it is necessary that the patient be checked at frequent intervals.   The low renal threshold makes it impossible to gauge the insulin requirements by the degree of glycosuria; therefore, repeated blood sugar determinations are necessary.

As mentioned above, the routine administration of diethylstilbestrol by the method of Smith, Smith and Hurwitz[56] is indicated.   We do not believe that routine Cesarean section is necessary.   The care of the new born infant, as outlined in the paragraph on neonatal death, is a phase which must not be neglected.

SUMMARY

1. A study of 450 pregnancies in 72 diabetics and prediabetics was made. The fetal mortality rate in the diabetic group was 54.7 per cent. During the years preceding the clinical diagnosis of diabetes, a high incidence of large babies, toxemia, stillbirths, neonatal deaths and spontaneous abortions was noted.   These complications were most marked during the five years immediately preceding the onset of diabetes, but definitely began 30 years before clinical diabetes was manifest.

2. The incidence of polyhydramnios and of spontaneous abortion is probably related to the control of diabetes; the other above mentioned complications are not.

3. Diethylstilbestrol was administered to six pregnant diabetics.   There were no fetal deaths in this treated group.   On the basis of other reports in the literature and this small series, it is felt that such treatment should be routine in all diabetic women as soon as they become pregnant.

4. The relation of "benign" renal glycosuria to latent or mild diabetes is discussed. It is probable that many diabetics masquerade under this diagnosis. In an effort to diagnose more cases of latent diabetes, it is suggested that a postprandial urine specimen be checked for glycosuria at each antepartum visit.

5. All patients with glycosuria, obesity or a family history of diabetes, or who have previously had one of the complications of pregnancy common to diabetics, should have a three hour glucose tolerance test.

BIBLIOGRAPHY

1. White, P.: *in* Joslin, E., et al.: Treatment of diabetes mellitus, ed. 8, 1947, Lea & Febiger, Inc., Philadelphia, pp. 769–784.
2. Eastman, N. J.: Diabetes mellitus and pregnancy, Obst. and Gynec. Surv. 1: 3–31, 1946.
3. Bowcock, H. M., and Greene, E. H.: Observations in a case of renal glycosuria, during and after pregnancy, J. A. M. A. 90: 502–504, 1928.
4. Skipper, E.: Diabetes mellitus and pregnancy, Quart. J. Med. 2: 353–380, 1933.
5. White, P.: Pregnancy complicating diabetes, Surg., Gynec. and Obst. 61: 324–332, 1935.
6. Miller, H. C., and Wilson, H. M.: Macrosomia, cardiac hypertrophy, erythroblastosis, and hyperplasia of the islets of Langerhans in infants born to diabetic mothers, J. Pediat. 23: 251–266, 1943.
7. Miller, H. C., Hurwitz, D., and Kuder, K.: Fetal and neonatal mortality in pregnancies complicated by diabetes mellitus, J. A. M. A. 124: 271–275, 1944.
8. Miller, H. C.: The effect of the prediabetic state on the survival of the fetus and the birthweight of the newborn infant, New England J. Med. 233: 376–378, 1945.
9. Miller, H. C.: The effect of diabetic and prediabetic pregnancies on the fetus and new-born infant, J. Pediat. 29: 455–461, 1946.
10. Dolger, H., and Herzstein, J.: Fetal and neonatal mortality complicated by diabetes, J. A. M. A. 125: 931, 1944.
11. Herzstein, J., and Dolger, H.: The fetal mortality in women during the prediabetic period, Am. J. Obst. and Gynec. 51: 420–422, 1946.
12. Patterson, M., and Burnstein, N.: Diabetes and pregnancy; a clinical analysis, Arch. Int. Med. 83: 390–401, 1949.
13. Barns, H. H. F., and Morgans, M. E.: Prediabetic pregnancy, J. Obst. and Gynaec. Brit. Emp. 55: 449–454, 1948.
14. Gilbert, J. A. L.: The association of maternal obesity, large babies and diabetes, Brit. M. J. 1: 702–704, 1949.
15. Herrick, W. W., and Tillman, A. J. B.: Diabetes and pregnancy, Surg., Gynec. and Obst. 66: 37–43, 1938
16. Kriss, J. P., and Futcher, P. H.: The relationship between infant birthweight and subsequent development of maternal diabetes mellitus, J. Clin. Endocrinol. 8: 380–389, 1948.
17. Paton, D. M.: Pregnancy in the prediabetic patient, Am. J. Obst. and Gynec. 56: 558–560, 1948.
18. Hamblen, E. C.: Endocrinology of woman, 1945, Charles Thomas Company, Springfield, Ill., p. 490.
19. Mengert, W. F., and Laughlin, K. A.: Thirty-three pregnancies in diabetic women, Surg., Gynec. and Obst. 69: 615–617, 1939.
20. Stander, H. J.: Textbook of obstetrics, ed. 9, 1945, D. Appleton-Century Co., New York, p. 727.
21. Englehardt, H. T., and Melvin, J. P., Jr.: The management of diabetes mellitus during pregnancy, South. M. J. 39: 734–737, 1946.

22. Allen, E.: The glycosurias of pregnancy, Am. J. Obst. and Gynec. **38**: 982–992, 1939.
23. Lawrence, R. D., and Oakley, W.: Pregnancy and diabetes, Quart. J. Med. **11**: 45–75, 1942.
24. Bill, A. H., and Posey, F. M.: Pregnancy and diabetes, Am. J. Obst. and Gynec. **48**: 405–408, 1944.
25. Randall, L. M.: Pregnancy associated with diabetes, Am. J. Obst. and Gynec. **54**: 618–625, 1947.
26. White, P.: Pregnancy complicating diabetes, J. A. M. A. **128**: 181–182, 1945.
27. Barns, H. H. F.: Diabetes mellitus and pregnancy, J. Obst. and Gynaec. Brit. Emp. **48**: 707–725, 1941.
28. Lavietes, P. H., Leary, D. C., Winkler, A. W., and Peters, J. P.: Diabetes mellitus and pregnancy, Yale J. Biol. and Med. **16**: 151–166, 1943.
29. Miller, H. C.: Cardiac hypertrophy in newborn infants, Yale J. Biol. and Med. **16**: 509–518, 1944.
30. Miller, H. C.: Cardiac hypertrophy and extra-medullary erythropoiesis in newborn infants of prediabetic mothers, Am. J. M. Sc. **209**: 447–455, 1945.
31. Miller, H. C., Johnson, R. D., and Durlacher, S. H.: A comparison of newborn infants with erythroblastosis fetalis with those born to diabetic mothers, J. Pediat. **24**: 603–615, 1944.
32. White, P.: Pregnancy complicating diabetes, Pennsylvania M. J. **50**: 705–708, 1947.
33. Odell, L. D., and Mengert, W. F.: The overweight obstetric patient, J. A. M. A. **128**: 87–90, 1945.
34. Gilbert, J. A. L., and Dunlop, D. M.: Diabetic fertility, maternal mortality and foetal loss rate, Brit. M. J. **1**: 48–51, 1949.
35. Barns, H. H. F., and Morgans, M. E.: Pregnancy complicated by diabetes mellitus, Brit. M. J. **1**: 51–54, 1949.
36. Ward, E. B.: Diabetes in pregnancy, J. M. Soc. New Jersey **43**: 267–268, 1946.
37. Hurwitz, D., and Irving, F. C.: Diabetes and pregnancy, Am. J. M. Sc. **194**: 85–92, 1937.
38. Bigby, M. A. M., and Jones, F. A.: Pregnancy and diabetes, Brit. M. J. **1**: 360–363, 1945.
39. Palmer, L. D., and Barnes, R. H.: Pregnancy in the diabetic, West. J. Surg. **53**: 195–202, 1945.
40. Casa Grande, J.: The postmature fetus, Am. J. Obst. and Gynec. **37**: 1028–1032, 1939.
41. Koff, A. K., and Potter, E. L.: The complications associated with excessive development of the human fetus, Am. J. Obst. and Gynec. **38**: 412–423, 1939.
42. Klein, J.: The relationship of maternal weight gain to the weight of the newborn infant, Am. J. Obst. and Gynec. **52**: 574–580, 1946.
43. Stander, H. J.: *Ibid.*, p. 916.
44. Stander, H. J.: *Ibid.*, p. 723.
45. Stander, H. J.: *Ibid.*, p. 673.
46. Stander, H. J.: *Ibid.*, p. 395.
47. Smith, O. W., and Smith, G. V. S.: Prolan and estrin in the serum and urine of diabetic and non-diabetic women during pregnancy, with especial reference to late pregnancy toxemia, Am. J. Obst. and Gynec. **33**: 365–379, 1937.
48. Smith, O. W., Smith, G. V. S., and Hurwitz, D.: The relationship between hormonal abnormalities and accidents of late pregnancy in diabetic women, Am. J. M. Sc. **208**: 25–35, 1944.
49. Smith, G. V. S., and Smith, O. W.: Toxemias of late pregnancy; endocrinologic aspects, résumé, Clinics **4**: 595–602, 1945.
50. White, P., and Hunt, H.: Pregnancy complicating diabetes; a report of clinical results, J. Clin. Endocrinol. **3**: 500–511, 1943.
51. Watts, R. M., and Adair, F. L.: Excretion of estrogen and gonadotropin in late pregnancy. With special reference to the toxemias of pregnancy and to quantitative methods, Am. J. Obst. and Gynec. **46**: 183–207, 1943.

52. Jordan, W. R.: Pregnancy and diabetes, Virginia M. Monthly **70**: 441–443, 1943.
53. Jordan, W. R.: Pregnancy and diabetes, Virginia M. Monthly **75**: 325–327, 1948.
54. Rubin, B. L., Dorfman, R. F., and Miller, M.: Hormone metabolites in blood and urine of diabetic patients with and without toxemia, J. Clin. Endocrinol. **6**: 347–368, 1946.
55. Bowen, B. D.: A primipara with diabetes and mild toxemia treated successfully with diethylstilbestrol, J. A. M. A. **126**: 98–99, 1944.
56. Smith, O. W., Smith, G. V. S., and Hurwitz, D.: Increased excretion of pregnandiol in pregnancy from diethylstilbestrol with special reference to the prevention of the late pregnancy accidents, Am. J. Obst. and Gynec. **51**: 411–415, 1946.
57. Palmer, L. J., Crampton, J. H., and Barnes, R. H.: Pregnancy in the diabetic, West. J. Surg. **56**: 175–177, 1948.
58. Gaspar, J. L.: Diabetes mellitus and pregnancy. A survey of 49 deliveries, West. J. Surg. **53**: 21–27, 1945.
59. Blotner, H.: Studies of glycosuria and diabetes mellitus in selectees, J. A. M. A. **131**: 1109–1114, 1946.
60. Wilkerson, H. L. C., and Krall, L. P.: Diabetes in a New England town, J. A. M. A. **135**: 209–216, 1947.
61. Ewald, P. P.: Pregnancy and diabetes, Journal Lancet **65**: 13–14, 1945.
62. Friedgood, C. E., and Miller, A. A.: Alloxan in pregnant rats, Proc. Soc. Exper. Biol. and Med. **59**: 61–62, 1945.
63. Miller, H. C.: The effect of pregnancy complicated by alloxan diabetes on the fetuses of dogs, rabbits and rats, Endocrinology **40**: 251–258, 1947.
64. Weiden, S.: Investigation of carbohydrate metabolism in normal pregnancy, M. J. Australia **1**: 646–651, 1948.
65. Archer, H. E., and Haram, B. J.: Reducing substances in the urine in pregnancy and the early puerperium, Lancet **1**: 558–559, 1948.
66. Bray, W. E.: Synopsis of clinical laboratory methods, ed. 1, 1944, C. V. Mosby Co., St. Louis, p. 47.
67. Hurwitz, D., and Jensen, D.: Carbohydrate metabolism in normal pregnancy, New England J. Med. **324**: 327–329, 1946.
68. Wilder, R. M.: The unknown diabetic and how to recognize him, J. A. M. A. **138**: 349–351, 1948.
69. Williams, E. C. P., and Wills, L.: Studies in blood and urinary chemistry during pregnancy, Quart. J. Med. **22**: 493–506, 1928–1929.
70. Richardson, R., and Bitter, R. S.: Glycosuria in pregnancy, Am. J. Obst. and Gynec. **24**: 363–369, 1932.
71. Johnson, D. G., and Bonsnes, R. W.: The intravenous glucose tolerance test in pregnancy, J. Clin. Investigation **27**: 745–748, 1948.
72. Bland, J. H.: Renal glycosuria; a review of the literature and report of four cases, Ann. Int. Med. **29**: 461–468, 1948.

TREATMENT OF TWO PATIENTS WITH HEPATO-RENAL SYNDROME AND ACUTE RENAL FAILURE BY EXSANGUINOTRANSFUSION [*]

By I. SNAPPER, M.D., and L. E. SCHAEFER, M.D., *New York, N. Y.*

AFTER exsanguinotransfusion had been tried and abandoned during the 17th century it was not used again until recently, when total replacement of blood was reintroduced by American clinicians for the treatment of fetal erythroblastosis. Bessis [1] in 1947 used exsanguinotransfusions in adults for the treatment of leukemia and later recommended the same method for the treatment of uremic patients, especially in cases of uremia due to acute anuria.[2] The quantities of dialyzable substances (urea, non-protein-nitrogen, etc.) removed during an exsanguinotransfusion are considerably smaller than those removed by the artificial kidney or with peritoneal irrigation.[3] Bessis himself reports that one exsanguinotransfusion usually does not reduce the urea nitrogen content of the blood: the 20 to 25 gm. of urea which are removed during the procedure are readily replaced by urea accumulated in the tissue fluids. However, nondialyzable toxic substances which may play a rôle in the etiology of uremia cannot be removed either by the artificial kidney or by peritoneal dialysis but are actually withdrawn during an exsanguinotransfusion. The French literature mentions several observations where exsanguinotransfusion apparently has been helpful in permitting survival until regeneration of the kidney tubules occurred.[4]

Usually, 7 to 8 liters of citrated blood are introduced and the same amount is withdrawn. It can be estimated that in this way nearly 80 per cent of the blood of the patient is replaced by normal blood. To prevent coagulation in the needles used for the exsanguinotransfusion, the patient is heparinized (100 to 200 mg.). The procedure in an adult takes about six hours. It should be remembered that each pint of citrated blood contains 120 c.c. of 4 per cent sodium citrate, and thus an exsanguinotransfusion also introduces large amounts of alkali. This, in patients with acidosis, is an added advantage. It is necessary to inject calcium gluconate intravenously during the procedure to prevent tetany due to fixation of the blood calcium by the large amounts of citrate.

We can report the favorable influence of exsanguinotransfusion in two cases of hepatorenal syndrome. In 1913 Merklen coined the name "hepatorenal syndrome" for the frequent occurrence of coincident hepatic and renal failure. Reasons for the rather commonly observed coincidence of liver and renal degeneration have been repeatedly discussed. During hepatitis and liver necrosis, the accumulation of large amounts of vasodepressor sub-

stances, which are always being formed in and detoxified by the liver, leads to a temporary vasomotor collapse.   The ischemia of the kidney resulting from this vasomotor paralysis is instrumental in the causation of tubular necrosis without much anatomic damage to the glomeruli (Penner and Bernheim,[6] Trueta and associates[7]).   The hypochloremia due to vomiting may also cause tubular damage.   During the collapse the function of the glomeruli is altered, as evidenced by the presence of protein in the glomerular capsular space, but after the collapse has subsided the glomeruli readily recover.   Since the blood supply to the tubules is derived from the glomerular blood flow, insufficient perfusion of the glomeruli must lead to damage of the tubules.   In contrast to the glomeruli, the tubules do not recover readily from anoxia.   Thus, during a vasomotor collapse, progressive necrobiotic changes of the convoluted tubules frequently develop.

The damage to the renal tubules is usually localized in the ascending part of Henle's loop and in the distal convoluted tubules (the so-called lower nephron).   This localization has given rise to the term "lower nephron nephrosis" by which this syndrome is designated.[8]   It should not be forgotten, however, that the proximal tubules may also be involved.   Lower nephron nephrosis is often the cause of acute oliguria and anuria.

Lucké[9] reported that in the majority of cases of liver necrosis at autopsy the kidneys were found to be swollen, flaccid and bile-stained.   Microscopically, in most cases, a "cholemic nephrosis" was found.   The glomeruli were well filled and had a normal cellularity, but protein was precipitated in the capsular spaces, indicating that the filtering capillaries were altered. Pigmented casts were found in various parts of the tubular system, particularly in the distal convoluted and collecting tubules.   The degenerative changes in the tubules varied from cloudy swelling to actual necrosis, comparable to the findings in mercury poisoning.   This cholemic nephrosis evidently represents a lower nephron nephrosis as found in fatal cases of hepatitis.   It may be noted that in Lucké's 31 fatal cases of fulminant hepatitis, in which death occurred three to 12 days after the jaundice had started, the kidney lesions were relatively minor.[10]

The occurrence of lower nephron nephrosis in acute liver necrosis leads to retention of non-protein-nitrogen and urea nitrogen in the blood serum. It should be added that the data available indicate that in cases of acute liver necrosis without anuria, but with considerable urea retention, the creatinine of the blood is usually only slightly increased.

At The Mount Sinai Hospital, 29 cases of acute liver necrosis came to autopsy.   In three cases the blood urea nitrogen was increased (40, 55 and 75 mg. per cent).   In the patient whose blood urea nitrogen had risen to 40 mg. per cent, the creatinine was found to be only moderately increased (2.4 mg. per cent).

Popper and his associates[11] report the results obtained in eight fatal cases of liver necrosis.   In one case the non-protein-nitrogen was normal;

in three cases it had risen to values between 40 and 70 mg. per cent, and in four cases more than 70 mg. per cent non-protein-nitrogen was found. The blood creatinine values of these patients were normal or slightly increased. The maximum found was 2.05 mg. per cent.

Umber [12] reports the results in seven fatal cases of acute liver necrosis. In three cases the non-protein-nitrogen content of the serum varied between 11 and 40 mg. per cent, the urea nitrogen between 7 and 22 mg. per cent, and the creatinine between 1 and 1.5 mg. per cent. In three other cases the non-protein-nitrogen was increased (57 and 70 mg. per cent), but the creatinine content was normal (1.8 and 1.3 mg. per cent). In another case, in which contracted kidneys were also found, the non-protein-nitrogen rose to 250 mg. per cent and the blood urea nitrogen to 60 mg. per cent, but no blood creatinine values are mentioned.

Lucké [9] found a normal non-protein-nitrogen content of the blood in 16 of 31 fatal cases; in 11 cases a slight increase (41 to 60 mg. per cent), and in four cases a marked increase (72, 75 and 103 mg. per cent). No creatinine values are given.

These figures indicate that in liver necrosis the high non-protein-nitrogen content is accompanied by a relatively normal creatinine content of the serum. Popper and his associates [11] attribute this discrepancy to the fact that the tubules are more damaged than the glomeruli. The damage to the tubules leads to increased reabsorption of nitrogenous substances through the damaged tubular barrier, which causes the urea and the non-protein-nitrogen retention. The glomeruli are relatively intact. As creatinine is excreted by the glomeruli and reabsorbed only minimally by the tubules, tubular damage will not, at least in the beginning, give rise to creatinine retention. Popper has practically proved his contention by demonstrating that in jaundice the creatinine clearance was relatively little damaged, compared to the urea clearance. It should be added that if anuria sets in, then, of course, all the water and substances dissolved in the glomerular filtrates, including creatinine, are reabsorbed. Thus when a hepatorenal syndrome leads to complete suppression of urine, not only the urea nitrogen and non-protein-nitrogen content of the serum, but also the creatinine content, rise to excessively high levels.

It cannot be sufficiently emphasized that in lower nephron nephrosis the glomeruli are histologically intact. The tubular lesion is purely epithelial in character and, as in all epithelial lesions, a complete recovery without scar formation is possible. When sufficient time is available, the necrotic tubules regenerate and a completely normal kidney results. It has been demonstrated that regeneration of the necrotic tubules starts after an average of 10 days. In most cases of lower nephron nephrosis, and therefore also of hepatorenal syndrome, spontaneous diuresis sets in after 10 days, and the severely uremic patients who often seem to be in a terminal condition recover. Thus, the purpose of the treatment of such patients consists of extending the survival period of the patient to 10 or 14 days.

The following two patients with hepatitis followed by extreme oliguria and severe uremia recovered, although their condition was seemingly desperate. In both cases diuresis started after exsanguinotransfusion. It cannot be proved that this fortunate sequence of events was actually due to the exsanguinotransfusion. .

CASE REPORTS

Case 1. A 65 year old woman was admitted to The Mount Sinai Hospital on November 10, 1948. She had always been well except for arthritis of many years' standing. Three months before admission she had had an acute disease which was diagnosed as gastroenteritis. No special treatment had been necessary, but since that time she had developed anorexia and generalized malaise and had lost 15 pounds in weight. Roentgenologic examination of stomach, duodenum, small intestine, colon and gall bladder did not reveal any abnormal findings except for diverticulosis coli. Two weeks before admission her temperature suddenly rose to 105° F. and nausea and vomiting occurred. She received penicillin and streptomycin and the temperature dropped to normal, but the nausea and vomiting continued. Ten days before admission she became markedly jaundiced. The jaundice persisted for five days and gradually decreased. In the meantime she became oliguric (140 to 180 c.c. per day), noted edema, and her blood pressure, which had always been around 130 mm. systolic, rose to 180. She was treated with large amounts of glucose and saline and received several blood transfusions. The blood urea nitrogen gradually increased. A very low albumin content of the serum and a marked leukocytosis varying between 30,000 and 42,000 white cells per cu. mm. were found (table 1). Gradually she became lethargic and almost unresponsive.

On admission she was acutely ill. The respirations were deep and rapid, the temperature 99° F., pulse 80, blood pressure 130 mm. Hg systolic and 70 mm. diastolic. Bilateral hemorrhagic scleritis and slight jaundice were present. The lungs showed a few crackles at both bases. The heart was enlarged to the left. There was a harsh precordial systolic murmur and a loud second aortic sound. The abdomen could not be palpated because there was marked edema of the abdominal wall. There was 4 plus edema of the extremities. No neurologic findings could be elicited.

The urine was acid, with a specific gravity of 1:010, a trace of albumin and a faint trace of bile. Microscopic examination was negative. The hemoglobin was 14 gm. per cent and the leukocytes totalled 17,900, with 65 per cent segmented polymorphonuclears, 20 per cent staff cells, 1 per cent myelocytes, 10 per cent lymphocytes and 4 per cent monocytes.

The blood urea nitrogen on admission was 85 mg. per cent, the serum chlorides 491 mg. per cent (as sodium chloride), the carbon dioxide combining power 24.4 vol. per cent, the alkaline phosphatase 48 King-Armstrong units per 100 c.c. Agglutination for *Leptospira icterohaemorrhagiae* was negative. Roentgen-ray of the abdomen showed that both kidneys were normal in size, shape and position. No stones were seen.

The patient ran a subfebrile temperature except for the third hospital day when, immediately after treatment with the artificial kidney, the temperature temporarily rose to 102° F. On the day after admission she was vomiting moderate amounts. The total urinary output was about 50 c.c., and she was much more drowsy. The blood urea nitrogen had risen to 117 mg. per cent, the blood non-protein-nitrogen to 161 mg. per cent, the creatinine to 10.2 mg. per cent. The CO_2 combining power was 25.1 vol. per cent, the serum chlorides were 515 mg. per cent. The thymol turbidity was 4 plus, the cephalin flocculation test 2 plus (table 1). After two days of almost complete anuria (daily urinary excretion 180 c.c. and 50 c.c.), the patient was

TABLE I

Hepatorenal Syndrome Treated with Dialysis in Artificial Kidney and Exsanguinotransfusion

Case I

Date	Urine c.c.	BUN Mg.%	NPN Mg.%	Creatinine Mg.%	Chlorides Mg.%	CO$_2$ Vol.%	Bilirubin Mg.%	Icterus Index	Cholesterol		Cephalin Floc.	Albumin Gm.%	Globulin Gm.%	Alkaline Phosphatase*	Leukocytes per cu. mm.
									Total Mg.%	Esters Mg.%					
1948															
Nov. 5	170						3.5	44							
6	140														
7	180														30,000
9	180	49		7.1		24.4		24	266	122	4+	1.45	2.41		42,000
10	180	85		10.2	491	25.1									17,900
11	50	{ 117 / 106†	{ 161 / 128†	9.8†	{ 515 / 550†	29.4†					{ 2+ / 3+†	1.86	3.66	48	
12	7	88	135	9.0	497	29.0									88,000
13	70	{ 82 / 63‡	99‡	6.8‡	{ 497 / 527‡	{ 26.0 / 43.0‡		9			{ 3+ / 2+‡	{ 2.24 / 2.29‡	{ 3.15 / 2.61‡		47,000
14	460		140												
15	1970	80	142	9.8		48.0					4+	2.40	4.10		57,000
16	3700		96	6.2	503							2.51	3.30		25,000
19	3450	75	86	4.6	527	61.4						3.03	4.90	.32	19,000
20	2270	48	70	2.7	538	56.0									12,000
22	1240	43	60	2.2	577	53.0	0.9	6	500	290	3+				11,000
25	1360	34	61	1.5	592						2+				
Dec. 2	—	36	42								4+	2.77	5.13	57	
13	—	29		2.8							4+			48	
1949															
Feb. 7	—		47								3+	3.38	4.38	16	
Apr. 19	—	25	60									3.07	5.56		
Sept. 15	—		49			1.0					1+	3.89	3.30		

* King-Armstrong units per 100 c.c. serum.
† After treatment with the artificial kidney.
‡ After exsanguinotransfusion.

dialyzed with the artificial kidney for two hours and forty-five minutes. During this procedure she went into left ventricular failure and the dialysis had to be stopped. The pulmonary edema responded to treatment, although slowly. The next day the leukocytes rose to 88,000, with a marked shift to the left. The blood urea nitrogen had decreased to 88 mg. per cent, the creatinine content to 9 mg. per cent. The CO_2 combining power was 29 vol. per cent.

Two days after the treatment with the artificial kidney the urinary output was only 70 c.c. The non-protein-nitrogen content of the blood was still 135 mg. per cent and the creatinine content 9 mg. per cent. An exsanguinotransfusion was therefore performed. Fifteen pints of blood were given and 14 pints withdrawn. The patient tolerated this procedure without any untoward effects. The day after the exsanguinotransfusion, diuresis began. This was progressive in nature. Two days after the exsanguinotransfusion the blood urea nitrogen was still 80 mg. per cent and the non-protein-nitrogen 140 mg. per cent. However, the CO_2 combining power had risen to 48 vol. per cent. On the sixth day after the exsanguinotransfusion, the edema had disappeared and the blood urea nitrogen was still 75 mg. per cent, but the non-protein-nitrogen had decreased to 96 mg. per cent and the creatinine to 6.2 mg. per cent. The white count had dropped to 12,000, with a normal differential.

Three weeks after admission the liver was felt four fingerbreadths below the costal margin and on some occasions the tip of the spleen was palpated. Damage of liver function was still evident; the cephalin flocculation test was 3 to 4 plus, the thymol turbidity 4 plus, the alkaline phosphatase 57 King-Armstrong units, and the bromsulfalein test revealed a retention of 32 per cent and 41 per cent after 45 minutes. The albumin content of the serum was 2.77 gm. per cent, the globulin content 5.13.

Six weeks after admission the patient was discharged with a blood urea nitrogen of 21 mg. per cent, a cephalin flocculation of 2 plus, and a thymol turbidity of 3 plus. The alkaline phosphatase was 32 King-Armstrong units per 100 c.c. of serum and the globulin content of the serum was still increased. The urine was normal. The hemoglobin was 11.6 mg. per cent, with 12,000 white blood cells. A concentration test showed the specific gravity of the urine to range between 1:012 and 1:017, and the phenolsulfonphthalein test showed an excretion of 45 per cent of the dye in three hours. Four months after discharge the serum chemistries were about the same. Ten months after the disease had set in the non-protein-nitrogen was only slightly increased (49 mg. per cent), the albumin was 3.89 gm. per cent, and the globulin was 3.30 gm. per cent. The cephalin flocculation test had also become normal (1 plus).

It was felt that this patient had suffered from an hepatorenal syndrome brought about by an acute hepatitis.

This case permits a comparison between the effect of a dialysis of the blood in the artificial kidney and the results of an exchange transfusion. The amounts of urea and other nitrogen-containing substances removed during dialysis are much larger.   The influence on the albumin and globulin content of the serum is not significant after either procedure (table 2). As in other patients in whom exsanguinotransfusion was performed, the increase of the blood proteins was only small at best.   This is in agreement with other evidence indicating that the capillaries in lungs, liver and the visceral lymph vessels are easily permeable to albumin.   The carbon dioxide combining power of the serum, which, as is well known, does not change after dialysis, improved considerably after the exchange transfusion, probably due to the sodium citrate present in the transfused blood.   It is diffi-

TABLE II

Hepatorenal Syndrome

Case 1

Dialysis in Artificial Kidney—11/11/48

	BUN Mg.%	Urea Mg.%	NPN Mg.%	Uric Acid Mg.%	Creati- nine Mg.%	Chlo- rides Mg.%	CO₂ Vol.%	Albu- min Gm.%	Glob- ulin Gm.%	Ceph- alin Floc.	Thymol Turb.
Before	117	252	161	14.9	10.2	505	25.1	1.86	3.66	2+	3+
After	106	228	128	10.2	9.8	550	29.4			3+	4+
Total Nitrogenous Substances Re- moved in Grams	27	58	37	4.5	3.5						

Exchange Transfusion—11/13/49

	BUN Mg.%	Urea Mg.%	NPN Mg.%	Uric Acid Mg.%	Creati- nine Mg.%	Chlo- rides Mg.%	CO₂ Vol.%	Albu- min Gm.%	Glob- ulin Gm.%	Ceph- alin Floc.	Thymol Turb.
Before	82	176	135	19.4	9.0	497	26.0	2.24	3.15	3+	4+
After	63	135	99	14.0	6.8	527	43.0	2.29	2.61	2+	3+
Total Nitrogenous Substances Re- moved in Grams	6.4	13.8	8.0	0.8	0.5						

cult to decide whether the fact that diuresis started after the exchange trans-fusion was coincidental.

Case 2. A 40 year old woman was admitted to The Mount Sinai Hospital on November 19, 1948. She had been apparently well until 1945, when she developed abdominal pain, nausea, vomiting, chills and fever. A diagnosis of cholecystitis was made, and a cholecystectomy was performed. Cholecystitis without stones was found. Since the operation she had had similar attacks once or twice per year, usually with-out chills or fever. She had had no jaundice at any time in the past.

For many years she had been drinking vodka liberally, several glasses per day. Ten days previous to admission to The Mount Sinai Hospital she began to have crampy abdominal pains, with spasm of the hands. Eight days before admission jaundice was noted. She then entered another hospital because a common duct stone was suspected. She had anorexia and vomited frequently, and her urinary output was extremely small, varying between 150 and 200 c.c. daily, notwithstanding large amounts of fluid injected intravenously. On the day before admission the non-protein-nitrogen had risen to 151 mg. per cent. The inorganic phosphorus of the blood was reported to be 8.9 mg. per cent, cholesterol 267 mg. per cent, with only 67 mg. of esters, alkaline phosphatase 6 and 9 King-Armstrong units (table 3).

On admission to The Mount Sinai Hospital the patient was drowsy but responded to questions. She was slightly icteric. Her blood pressure was 100 mm. Hg systolic and 65 mm. diastolic, temperature 104° F., pulse 92, respirations 60. Physical find-ings were negative except for a sharp, firm liver which was felt one fingerbreadth below the costal margin. The spleen was not palpable. There was no ascites or edema.

Compared with the reported findings of the previous day, the general condition of the patient seemed to be deteriorating. Blood urea nitrogen was 114 mg. per cent, non-protein-nitrogen 150 mg. per cent, creatinine 12 mg. per cent, CO₂ combining

TABLE III

Hepatorenal Syndrome Treated with Exsanguinotransfusion

Case 2

Date	Output	BUN Mg.%	NPN Mg.%	Uric Acid Mg.%	Creatinine Mg.%	Icterus Index	Bilirubin Mg.%	Cephalin Floc.	Thymol Turb.	Albumin Gm.%	Globulin Gm.%	Total Protein Gm.%	Chlorides Mg.%	CO_2 Vol.%	Alk. Phosphatase per 100 c.c.*	Leukocytes per cu. mm.
1948																
Nov. 16	200	—	160	—	—	—	9.2	—	—	—	—	6.6	—	—	—	13,000
17	150	—	—	—	—	—	—	—	—	—	—	—	—	—	6	
18	250	—	151	—	—	—	—	—	—	—	—	—	—	—	9	20,700
I 19	250	114 / 70†	150 / 101†	15.6 / 8.4†	12.0 / 8.2†	—	—	—	—	2.28 / 2.79†	3.50 / 2.22†	5.78 / 5.01†	491	44 / 58†	—	21,000
20	1320	97	128	15.6	10.5	—	—	4+	2+	3.68	2.11	5.79	480	68	—	18,000
21	1940	—	124	7.8	6.7	—	—	—	—	3.55	3.19	6.74	—	71.5	—	
22	1220	82	110	6.0	3.8	—	1.7	—	—	—	—	—	550	—	—	
II 23	1080	64 / 48‡	83 / 69‡	3.5‡	3.3‡	—	—	—	—	2.54 / 3.37‡	3.37 / 2.81‡	5.91 / 6.18‡	—	—	—	21,000
24	950	—	—	—	—	24	4.5	2+	4+	—	—	6.20	—	—	—	
25	1090	18	39	4.6	2.3	—	0.8	—	3+	2.81	3.95	6.6	—	—	35	22,000
26	980	14	34	4.2	2.5	—	1.0	3+	3+	3.50	4.37	7.87	—	—	42	
Dec. 1	970	14	35	—	—	—	—	—	—	—	—	—	—	—	—	
13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
1949																
Jan. 17	—	20	40	—	1.7	—	—	3+	4+	3.84	3.24	7.08	—	—	14	
May	—	—	—	—	—	—	—	1+	3+	—	—	—	—	—	—	

* King-Armstrong units.
† After first exsanguinotransfusion.
‡ After second exsanguinotransfusion.
I First exsanguinotransfusion.
II Second exsanguinotransfusion.

power 44 vol. per cent. The hemoglobin was 13.3 gm., red blood count 4,580,000, white blood count 20,700, with 26 per cent staff cells. Exsanguinotransfusion with 14 pints of blood was performed. The procedure took three and one-half hours. Shortly after starting the transfusion urticaria developed, for which epinephrine was given. As the fourteenth pint of blood was flowing in, the patient complained of some difficulty in breathing. It had been planned to give a fifteenth pint but this was withheld. At the completion of the exsanguinotransfusion, the patient became flushed and had a chill. The temperature rose to 104° F., as it had the night before the transfusion. Immediately after the exchange the blood urea nitrogen had diminished from 114 to 70 mg. per cent, the non-protein-nitrogen from 150 to 101 mg. per cent, and the creatinine from 12 to 8.2 mg. per cent (table 3). The next day the patient had less air-hunger and was more alert. The liver was felt two fingerbreadths below the costal margin. At the same time diuresis started. Between midnight after the exsanguinotransfusion and the next morning at 8:30, 480 c.c. of urine had been produced. During the next two days the urinary output increased to about 2,000 c.c. per day. The temperature was still 103.2° F., the white blood count 18,400. On November 21, two days after the exchange transfusion, the non-protein-nitrogen of the blood had increased to 124 mg. per cent. The next day the blood urea nitrogen was 82 mg. per cent, the non-protein-nitrogen 110 mg. per cent, serum chlorides 550 mg. per cent, CO_2 combining power 71.5 vol. per cent. Four days after the procedure, when the complete chemistries of preceding day were not yet available, the general condition seemed worse and the sensorium less clear. For this reason another exsanguinotransfusion of 10 pints of blood was performed. Afterwards it appeared that, as far as the blood chemistry was concerned, the patient had already been improving before the second exsanguinotransfusion. After this second procedure the condition of the patient improved rapidly. The next day the temperature came down to normal.

On November 27, the white blood cells were 21,000, the urine still showed a positive bile reaction, and the urobilinogen was 1:80.

On December 3, there was only a faint trace of bile in the urine, with 1:160 urobilinogen. The serum bilirubin had come down to normal levels. The white blood cells had decreased to 13,000. On December 7 a phenolsulfonphthalein test was performed which showed that only 30 per cent of the dye was excreted in the course of two hours. The bromsulfalein test showed 39 per cent retention after 45 minutes, whereas the bilirubin content of the serum was normal (0.8 mg. per cent). The cephalin flocculation test was 4 plus, the alkaline phosphatase 42 King-Armstrong units per 100 c.c., and other liver tests also indicated severe hepatocellular damage.

After the patient was discharged she no longer had any complaints. On January 17, 1949, the non-protein-nitrogen of the blood was 40 mg. per cent, creatinine 1.7 mg. per cent, alkaline phosphatase 14 King-Armstrong units per 100 c.c. There was still evidence of liver damage as the cephalin flocculation and thymol turbidity reactions were 3 plus and 4 plus, respectively. The serum albumin was 3.84 gm. per cent, the globulin 3.24 gm. per cent. The liver was two fingerbreadths below the costal margin, the spleen was just palpable. In May, 1949, the urea nitrogen was 20 mg. per cent, the cephalin flocculation 1 plus, the thymol turbidity still 3 plus. The liver was only one fingerbreadth below the costal margin, smooth, and with a normal consistency. The spleen could no longer be felt.

In this patient the biochemistry of the blood improved considerably after both the first and the second exchange transfusions. Again it appears that the quantities of nitrogenous substances removed during a dialysis in the artificial kidney are much larger than during an exchange transfusion. The figures obtained during the second exchange transfusion show that the

TABLE IV

Hepatorenal Syndrome

Case 2

First Exchange Transfusion—11/19/48
8,105 c.c.—Blood out
7,000 c.c.—Blood in

	BUN Mg.%	Urea Mg.%	NPN Mg.%	Uric Acid Mg.%	Creatinine Mg.%	Chlorides Mg.%	CO_2 Vol.%	Albumin Gm.%	Globulin Gm.%	Total Protein Gm.%	Ceph. Floc.	Thymol Turb.	Tyrosin Mg.%
Before	114	245	150	15.6	12.0	480	44	2.28	3.50	5.78		3+	3.2
During	101	217	124	8.6	9.0	491	46	3.55	3.19	6.66		2+	2.4
After	70	151	101	6.4	8.2	491	58	2.79	2.22	5.01		2+	2.2
Total Nitrogenous Substances Removed in Grams	7.26	15.6	8.26	1.05	0.75								

Second Exchange Transfusion—11/23/48
5,060 c.c.—Blood out
5,000 c.c.—Blood in

	BUN Mg.%	Urea Mg.%	NPN Mg.%	Uric Acid Mg.%	Creatinine Mg.%	Chlorides Mg.%	CO_2 Vol.%	Albumin Gm.%	Globulin Gm.%	Total Protein Gm.%	Ceph. Floc.	Thymol Turb.	Tyrosin Mg.%
Before	64	137	83	6.0	3.8			2.54	3.37	5.91		2+	3.2
During	61	131	80	6.1	3.5					5.70		1+	2.2
After	48	103	69	3.5	3.3			3.37	2.81	6.18		0	1.8
Total Nitrogenous Substances Removed in Grams	0.52	1.07	1.59	.06	.12								

quantity of nitrogenous products removed in a patient with a moderate urea nitrogen retention is insignificant (table 4). After the first exchange transfusion, the albumin content of the blood serum increased somewhat and the globulin content decreased. After the second exchange transfusion, the albumin content of the blood serum improved somewhat more. Again, as discussed above, the increase of the albumin content of the serum after an exchange transfusion is quite small. On the other hand, the increase of the carbon dioxide combining power of the blood is marked, due probably to the sodium citrate content of the transfused blood.

Both cases of hepatorenal syndrome showed a marked leukocytosis. This has been observed before. Umber [12] mentions that leukocytosis was occasionally seen in his seven cases of liver necrosis. In the report on the 1922 outbreak of postarsphenamine hepatitis in the Cherry Linton Hospital,[13] four white counts were given. Three fatal cases had 14,000, 17,000,

TABLE V

Leukocyte Count in 10 Cases of Acute Liver Necrosis, Autopsied at the Mount Sinai Hospital

	Age	Sex	White Blood Count	BUN (Mg.%)	Remarks
1.	50	F	18,000	10	—
2.	57	F	28,000	40	Creatinine 2.4 mg.%
3.	57	F	22,000	17	Uric acid 1.4 mg.%
4.	38	F	16,000	9	—
5.	38	F	25,000	10	Subphrenic abscess
6.	28	M	36,000	16	—
7.	1½	M	26,000	10	—
8.	72	M	31,500	24	—
9.	65	F	20,750	8	Pyometra
10.	34	M	68,000	10	—

and 20,000 leukocytes; one case that survived, 16,000. The most extensive material has been analyzed by Lucké.[9] He found that the majority of his 125 fatal cases had a mild leukocytosis, five had a count greater than 15,000, and one showed 31,000 leukocytes. Study of 10 patients with acute yellow liver atrophy that came to autopsy at The Mount Sinai Hospital also showed that most of the cases had leukocytosis (table 5). Of the 10 cases listed, cases 5 and 9 had a complicating illness which could have produced in itself a leukocytosis of the magnitude reported. Of the remaining eight, however, there was no complicating condition which could have given rise to such high white counts.

It follows, therefore, that leukocytosis is a frequently seen sign in acute liver necrosis.

SUMMARY

Exsanguinotransfusion in adults consists of the introduction of 7 to 8 liters of citrated blood and the withdrawal of the same amount. This method, as advocated by Bessis for the treatment of uremia, has been applied

by us to two patients suffering from an hepatorenal syndrome with extreme oliguria and severe uremia following hepatitis.

In both patients the daily urinary secretion had for several days varied between 100 and 200 c.c.; the blood non-protein-nitrogen had risen to 150 mg. per cent, the urea nitrogen to around 110 mg. per cent, and the creatinine to about 10 mg. per cent. In one patient a dialysis in the artificial kidney was performed first. When on the next day the urinary secretion had decreased to 7 c.c. and the general condition had deteriorated, an exsanguinotransfusion was performed. Diuresis started the next day and the patient recovered.

In the second patient, two exsanguinotransfusions were performed. After the first operation diuresis set in. In order to improve the general condition, a second exsanguinotransfusion was given four days later. The possibility that exsanguinotransfusion may be valuable in patients with a hepatorenal syndrome must be seriously considered. In this condition the protein content of the blood and probably also of the tissue fluid of the visceral organs is so severely altered that introduction of large amounts of normal blood proteins seems a reasonable treatment. The amounts of alkali which the citrated transfusion blood contains may also be a favorable side issue of the exsanguinotransfusion.

It must be stated that in both our patients, after the exsanguinotransfusion, the improvement of the blood proteins was insignificant. This is not surprising, since the capillaries of liver and lung and also the visceral lymph vessels are easily permeable for albumin. It was many months before the albumin and globulin content of the blood serum returned to normal values.

BIBLIOGRAPHY

1. Bessis, M., and Bernard, J.: Remarquables résultats du traitement par l'exsanguino-transfusion d'un cas de leucémie aiguë, Bull. et mém. Soc. méd. d. hôp. de Paris 63: 871, 1947.

2. Bessis, M., and Bernard, J.: Indications de l'exsanguino-transfusion en dehors de la maladie hémolytique de nouveau-né, Sang 19: 40, 1948.

   Bessis, M.: The use of replacement transfusion in diseases other than hemolytic disease of the newborn, Blood 4: 324, 1949.

   Bessis, M.: L'exsanguino-transfusion en dehors de la maladie hémolytique du nouveau-né, Extrait des Acquisitions Médicales Récentes, 1948.

3. Snapper, I.: Management of acute renal failure, Bull. New York Acad. Med. 25: 199, 1949.

   Snapper, I.: Medical clinics on bone diseases, ed. 2, 1949, Interscience Publishers, Inc., New York.

4. Vallery-Radot, P., Milliez, P., Laroche, C., Lhermitte, F., and Levasseur, C.: Première observation de néphrite aiguë azotémique indiscutablement guerie par la méthode de Bessis, Bull. et mém. Soc. méd. d. hôp. de Paris 64: 563, 1948.

   Tzanck, A., and Dausset, J.: L'exsanguino-transfusion dans les anuries, Bull. et mém. Soc. méd. d. hôp. de Paris 64: 563, 1948.

5. Shorr, E., Zweifach, B. W., and Furchgott, R. F.: Hepato-renal factors in circulatory homeostasis, Ann. New York Acad. Sc. 49: 571, 1948.

6. Penner, A., and Bernheim, A.: Acute ischemic necrosis of the kidney, Arch. Path. 30 465, 1940.

7. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. L.: Studies of the renal circulation, 1947, C. C. Thomas, Springfield, Illinois.

8. Lucké, B.: Lower nephron nephrosis (the renal lesions of the crush syndrome of burns, transfusions, and other conditions affecting the lower segment of the nephrons), Mil. Surgeon 99: 371, 1946.

9. Lucké, B.: Pathology of fatal epidemic hepatitis, Am. J. Path. 20: 471, 1944.

10. Lucké, B., and Mallory, T.: Fulminant form of epidemic hepatitis, Am. J. Path. 22: 867, 1946.

11. Meyer, K. A., Popper, H., and Steigmann, F.: Significance of rise of nonprotein nitrogen in medical and surgical jaundice, J. A. M. A. 117: 847, 1941.

12. Umber, F.: Zur akuten Leberatrophie, Berl. klin. Wchnschr. 57: 125, 1920.
    Umber, F.: Erkrankungen der Leber, der Gallenwege und des Pankreas, Handb. d. inn. Med., 2nd Ed., Vol. 3, 1926, Edited by Bergman and Staebelin, Julius Springer, Berlin.

13. Reports of the Salvarsan Committee. II. Toxic effects following employment of arseno-benzol preparations, Great Britain Medical Research Council, Special Report Series, Number 66, 1922.

VIRUS ENCEPHALITIS DURING A POLIOMYELITIS EPIDEMIC: A REPORT OF FIVE CASES [*]

By I. Dravin, M.D., J. H. Coffey, M.D., and W. C. Dine, M.D., F.A.C.P.,
Amarillo, Texas

We have recently had occasion to study five cases of virus encephalitis admitted within a six week period during a moderately severe epidemic of poliomyelitis. Four of these were identified as western equine encephalitis and one as St. Louis encephalitis by complement fixation and neutralizing antibody studies.[†]

A filtrable virus was found in 1924 to be the cause of a mild form of equine encephalomyelitis of horses, known in Europe for many years as Borna disease. A similar condition had also been noted in the United States for many years, but it was not until 1930 that the virus was isolated from the brains of two horses dying of the disease in the San Joaquin Valley.[2] Since 1930, the virus has been isolated from horses in 19 states,[3, 4] including Texas, with a peak of 184,662 cases in 1938.[5] Karl Meyer[6] first suspected that the virus of equine encephalomyelitis might be a cause of human encephalitis. He showed pathologic lesions similar to those in horses in a ranch hand dying of encephalitis, but did not, however, isolate the virus or demonstrate neutralizing antibodies. It remained for Howitt[7] to isolate the virus of western equine encephalitis from the brain of a 20 month old infant dying in California. Shortly before this, Fothergill[8] had isolated, from a child dying in Boston, a virus which was identified by cross-protection tests as the virus of eastern equine encephalitis. This was confirmed by the complement fixation test.[9] The largest epidemic of western equine encephalitis occurred in 1941, chiefly in North Dakota, Minnesota and adjacent Canadian provinces, where over 3,000 persons were stricken, with a mortality rate of 8 to 15 per cent.[10] There have been annual outbreaks in the Yakima Valley[11, 12] and in Kern and Fresno Counties in California.[13, 14] There have also been sporadic, isolated cases reported from time to time,[15, 16] and infection of laboratory workers handling chick embryos infected with western equine encephalomyelitis has been reported.[17, 18]

Experimentally, several species of mosquitoes,[19] the conenose bug (*Triatoma sanguisuga*)[20] and the wood-tick (*Dermacentor andersoni*)[21] can be infected and can transmit the virus of western equine encephalomyelitis to various laboratory animals. *Culex tarsalis* mosquitoes,[22] the conenose

bug (*Triatoma sanguisuga*),[20] the chicken mite (*Dermanyssus gallinae*),[23] and wild-bird mites (*Liponyssus sylviarum*) [24] have been found infected in nature.   In addition to horses, chickens and other fowl are believed to be the natural reservoir of the virus.[10]   An infected deer [25] and hog [26] have been reported.

In the summer of 1933, an epidemic of encephalitis occurred in and around St. Louis and Kansas City, Missouri, with 1,130 cases reported in St. Louis County.   Muckenfuss, Armstrong and McCordock recovered the causal virus by inoculation of infected brain tissue into monkeys.   Since the original St. Louis epidemic there have been minor epidemics,[28] including some due to both St. Louis and western equine types [11, 29] and another major epidemic in St. Louis in 1937.[30]

It is now generally accepted [31] that the St. Louis type of virus encephalitis is frequently transmitted to man by the bite of mosquitoes that have become infected, usually by feeding on recently infected fowl.   However, the true reservoir still has not definitely been determined, and may be a tick or a mite.

The clinical pictures of western equine and St. Louis encephalitis are indistinguishable.   The incubation period varies from four to 21 days in each.   Commonly, there are prodromata of headache, drowsiness, fever and gastrointestinal disturbances, followed by severe headache, insomnia, vertigo, nuchal rigidity and Kernig's sign.   Lethargy, disturbance of speech, ataxia, nystagmus, tremor, convulsions, mental confusion, amnesia and even coma may occur.   Paralysis is not common, occurring in about 15 per cent and usually being spastic.   Ophthalmoplegia and ptosis are still rarer, and more apt to occur in the equine type.   Abortive forms occur, ranging from subclinical infections to the presence of some of the prodromata.   The acute febrile phase usually lasts seven to 10 days.   There is usually complete recovery, with residuals such as Parkinsonism, hydrocephalus, mental retardation and epileptiform seizures occurring in less than 5 per cent.[10]   However, in some outbreaks of the St. Louis type, 10 to 40 per cent of infants showed these permanent sequelae.   In both types, the blood shows a moderate leukocytosis.   The spinal fluid may show a normal cell count [16] or a pleocytosis up to 300 to 400 cells, with polymorphonuclear cells predominating for about the first three days, and then giving way to mononuclear cells.   Protein is usually increased.   Spinal fluid glucose is normal.

The definitive diagnosis of western equine and St. Louis encephalitis depends upon the neutralization and complement fixation tests.   Ideally for the former, specimens should be obtained as early as possible during the acute phase of the disease, a second, one or two weeks after onset, and a third, if necessary, three to eight weeks after onset.   A rising titer is diagnostic.   The complement fixation test is more satisfactory,[31] but thus far has not been accepted for general use.   The technical aspects of these tests, as well as the method for obtaining and transporting serum for the tests,[31] are beyond the scope of this paper.

The treatment of western equine and St. Louis encephalitis is symptomatic, although horse antiserum [18] and gamma globulin [16] have been used with equivocal results. Only rarely will the diagnosis be made in sporadic cases in time to utilize such agents.

CASE REPORTS

Case 1. A 21 year old white unemployed male resident of Amarillo, Texas, was admitted June 29, 1949, complaining of severe headache, fever, chills, back pain and weakness of one week's duration. Physical examination revealed a muscular white male who was acutely ill, drowsy and apathetic. Temperature was 102° F. orally, pulse 120, and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. There was moderate nuchal rigidity. The pupils were equal, but the right pupil reacted poorly to light. Ophthalmoscopic examination revealed bilateral blurring of the disc margins. There was an unsustained bilateral ankle clonus, but knee and ankle jerks were within normal limits and there were no pathologic toe reflexes. Kernig's sign was positive.

Laboratory Studies: White blood count on admission was 8,300. On the following day it was 6,100, of which 69 per cent were neutrophils, 21 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. Hemoglobin was 13.9 gm. per 100 c.c. Serologic tests for syphilis and agglutinations were negative. Roentgenogram of the chest was negative. Spinal fluid examination on admission revealed clear fluid at a pressure of 150 mm., a cell count of 3 lymphocytes and 1 neutrophil, a 1 plus globulin, 40 mg. per cent protein, and negative culture and complement fixation test. The gold curve was 2233100000. On July 1, a second examination revealed clear fluid at a pressure of 280 mm., a cell count of 69, of which almost all were polymorphonuclear leukocytes, 1 plus globulin, chlorides of 740 mg. per cent, and negative complement fixation test for syphilis: culture of the fluid was negative. Gold curve was 1200000000. A serum specimen drawn July 7 was negative for complement fixing and neutralizing antibodies of western equine encephalitis, but the specimen drawn August 1 was positive for both.

Course: Treatment consisted of an indwelling catheter, large doses of penicillin and parenteral fluids. The patient became lethargic and semicomatose and remained so for a week, during which time he was extremely ill, with fever as high as 104° F. rectally, marked nuchal rigidity and cogwheel rigidity of the right upper extremity. Following this period he improved, became afebrile, but developed diplopia and a marked intention tremor of both hands. These gradually improved and at the time of discharge, July 30, there was only a very slight tremor and no diplopia.

Case 2. A 53 year old white male farmer, a resident of Hereford, Texas, was admitted July 28, 1949, complaining of severe, generalized headache, fever, chilly sensations, nausea and anorexia of two days' duration. There was a drawing sensation between the scapulae but no complaint of stiff neck.

Physical examination revealed a well nourished and well developed white male appearing ill. Temperature was 100.4° F. orally, pulse 80, blood pressure 130 mm. Hg systolic and 80 mm. diastolic. Other than slight nuchal rigidity, the physical and neurologic examinations were negative.

Laboratory Studies: Complete blood count, malaria smear, urinalysis, serologic test for syphilis, agglutinations for *E. typhosa,* salmonella group, and *B. melitensis,* blood cultures and chest roentgenogram were negative. Spinal fluid examination shortly after admission revealed clear fluid, a cell count of 166 per cu. mm. of which 60 per cent were polymorphonuclear leukocytes and 40 per cent lymphocytes, negative globulin and culture, and a total protein of 35 mg. per cent. Gold curve was

0012100000.   A second examination on August 8 revealed clear fluid, with 26 neutrophils per cu. mm. and a third examination on August 24 revealed 6 neutrophils per cu. mm.   Virus studies showed no complement fixing antibodies for lymphocytic choriomeningitis, mumps, or eastern or western encephalomyelitis, and no neutralizing antibodies for St. Louis encephalitis.   Sera drawn on the tenth and thirty-first days of the illness were both positive for neutralizing antibodies of western equine encephalitis.

Course: The patient complained of headache and stiff neck for the week after admission, during which time he received codeine, penicillin and sulfadiazine.   He was afebrile after the fifth hospital day and was discharged entirely asymptomatic on August 27.

Case 3.   A 21 year old white male transient was brought to the hospital on August 8, 1949, in a disoriented state, and no history was available.   It was later ascertained that he was an itinerant worker and had become acutely ill on the day before admission, with high fever, visual hallucinations and complete disorientation.

Physical examination on admission revealed a temperature of 103° F. orally, pulse 88, and blood pressure of 100 mm. Hg systolic and 60 mm. diastolic.   The patient was completely disoriented and delirious.   There was slight nuchal rigidity, slight weakness of the right upper and lower extremities, and the toe signs on the right were extensor.   The physical and neurologic examinations were otherwise not remarkable.

Laboratory Studies: Complete blood count revealed 12,150 white blood cells, of which 69 per cent were neutrophils, 24 per cent were lymphocytes, and 7 per cent monocytes, and 14.75 gm. hemoglobin per 100 cu. mm.   Urinalysis, serologic test for syphilis and chest roentgenogram were negative.   Spinal fluid examination on admission revealed slightly cloudy fluid, 111 cells per cubic millimeter, of which six were neutrophils and 105 were lymphocytes, and total protein of 22 mg. per cent.   Tests for neutralizing antibodies for western equine encephalitis were positive on specimens of serum drawn on August 15 and August 23, with a definite rise in titer in the second specimen.

Course: The patient was critically ill, febrile, disoriented and delirious for the week following admission.   On August 10 there was marked nuchal rigidity, a right hemiparesis, and marked spasticity and tremor involving the left side of the body.   On one occasion the patient was thought by the nurse to have died.   He received intravenous fluids, penicillin and sedation.   After the stormy first week of hospitalization he became afebrile, gradually improved, and was discharged asymptomatic on August 24.

Case 4.   A 57 year old white male safety engineer, a resident of Amarillo, Texas, was admitted August 11, 1949, complaining of weakness, dizzy spells and ankle edema.   He had had diabetes mellitus for 25 years, regulated on an 1,800 calorie diet and 40 units of protamine zinc insulin daily.   On previous admissions he had been found to have the Kimmelstiel-Wilson syndrome, with hypertension, retinopathy, albuminuria and edema.   Shortly before admission he had been hospitalized briefly and told that he had a "kidney infection."

Physical examination revealed a well nourished white male, appearing chronically ill.   Temperature was 98° F. orally, pulse 110, and blood pressure 190 mm. Hg systolic and 100 mm. diastolic.   Ophthalmoscopic examination revealed many small hemorrhages and exudates.   The liver was palpable just below the costal margin.   The neurologic examination was not remarkable except for the absence of knee and ankle jerks.   (This had been noted previously and ascribed to diabetic neuropathy.)

Laboratory Studies: Complete blood count, fasting blood sugar and non-protein-nitrogen were normal.   Urine was negative for sugar and acetone, but showed a 3 plus albumin and innumerable clumps of white blood cells.   However, urine cultures were negative, and smears of the urinary sediment failed to show any organisms.   Roentgenograms of the chest and abdomen were negative.   Spinal fluid examination

on August 18 revealed slightly cloudy fluid at a pressure of 260 mm., 241 cells per cu. mm., of which 91 per cent were neutrophils and 9 per cent lymphocytes, 1 plus globulin, total protein of 50 mg. per cent, and negative culture, complement fixation test, and gold curve. Serum drawn on August 26 was negative for complement fixing antibodies, but positive for neutralizing antibodies of western equine encephalitis. Serum drawn on September 13 was positive for both neutralizing and complement fixing antibodies.

Course: The patient was afebrile after the second hospital day, and was thought to have a genitourinary tract infection. On August 15 his temperature was 104° F. orally, and intramuscular penicillin therapy was begun. He continued to have fever and appeared toxic. On August 18 nuchal rigidity was noted for the first time. Spinal fluid examination was performed, with the previously noted findings. Treatment consisted of an 1,800 calorie diet and 30 to 40 units of protamine zinc insulin daily. He never developed acetonuria, and no parenteral fluids were given. He required large amounts of codeine to control his headache, and continued to be febrile until August 22, following which his only complaints were weakness, occasional headaches and some anorexia. These eventually disappeared and he was discharged September 13.

Case 5. A 25 year old white male oil field research worker, a resident of Lovington, New Mexico, was admitted August 9, 1949, complaining of malaise, chills, fever, headache, nausea, vomiting and backache of two weeks' duration. There was a past history of malaria, contracted while serving with the Army in the Pacific Theater, the last positive smear having been obtained two years prior to admission.

Physical examination revealed a well developed but acutely ill and apathetic white male. Temperature was 98° F. orally, pulse 72, blood pressure 110 mm. Hg systolic and 70 mm. diastolic. There were nuchal rigidity and a positive Kernig's sign. The remaining physical and neurologic examinations were negative.

Laboratory Studies: Complete blood count, urinalysis, chest roentgenogram, agglutinations for *E. typhosa,* salmonella group, and *B. melitensis,* serologic test for syphilis, and malaria smears were negative. Spinal fluid examination on admission showed slightly cloudy fluid at a pressure of 190 mm., 134 cells per cu. mm., almost all of which were polymorphonuclear leukocytes, 2 plus globulin and total protein of 22 mg. per 100 c.c. A second examination on August 15 showed 16 cells, 40 mg. per cent protein. Serum drawn on August 12 was negative for neutralizing antibodies for St. Louis encephalitis, but serum drawn September 13 was positive.

Course: The patient was afebrile following admission but complained of nausea, vomiting, headache and anorexia. He was given parenteral fluids, codeine, sedation and penicillin. He improved, and by August 23 was thought to have recovered sufficiently to be sent on leave. While on leave, however, he had a recrudescence of his symptoms of headache, nausea, and vomiting for several days. He returned from leave September 12, asymptomatic, and was discharged the following day.

DISCUSSION

It is of interest to note that four of the five cases had not been out of the Northwest Texas-Eastern New Mexico area for some time prior to the onset of their illness. It seems reasonable to suppose that there were other cases of virus encephalitis in this area during this time, although the lack of definitive diagnosis by serologic tests precludes any knowledge of the exact proportions of such a presumed epidemic. During the period in which our cases occurred, there were some 18 cases of poliomyelitis reported to the county health authorities. This epidemic of poliomyelitis was much more severe in other parts of Texas, however. Because of a similar seasonal

incidence, as well as the occurrence of many of the same clinical features in both diseases, it seems probable that many cases of virus encephalitis have been erroneously diagnosed as poliomyelitis. A spastic type of paraly is favors the diagnosis of encephalitis, but in nonparalytic forms serologic studies may be necessary for differentiation.

It occurred to us that possibly the increased rainfall in this area during this outbreak of St. Louis and western equine encephalitis might account for it by favoring the propagation of the vector, the mosquito. Whereas the normal rainfall for July in this area is 2.84 inches, it was 3.90 inches in 1949.

All of our cases recovered with only symptomatic nonspecific therapy, despite the fact that two were of extreme severity. Obviously, had any specific therapy been used, it would have received undue credit for the recoveries. This highlights the difficulty in evaluating the specific treatment of a disease occurring sporadically or infrequently. The newer antibiotics, aureomycin and chloramphenicol, were unavailable, but their use should be tried in future cases of virus encephalitis since certain other virus diseases have responded to them, especially to aureomycin.

These cases illustrate well the extreme variability in the severity of western equine encephalitis, from a mild infection such as occurred in case 2 to the extremely severe, fulminating course of cases 1 and 3.

SUMMARY

Five cases of virus encephalitis occurring during a poliomyelitis epidemic are reported. Four of these were proved serologically to be western equine and one the St. Louis variety.

BIBLIOGRAPHY

1. Moussu, R., and Marchand, L.: L'encephalite enzootique du cheval, Rec. I, Med. Vet. 100: 65, 1924.
2. Meyer, K. F., Horing, C. M., and Howitt, B.: Etiology of epizootic encephalomyelitis of horses in San Joaquin Valley, Science 74: 227, 1931.
3. Shahan, M. S., and Giltner, L. T.: Identity of viruses from cases of equine encephalomyelitis during 1942, J. Am. Vet. M. A. 102: 271–275, 1943.
4. Idem. Review of epizootiology of equine encephalomyelitis in United States, J. Am. Vet. M. A. 107: 279–288, 1945.
5. Mohler, J. R.: Reports on infectious equine encephalomyelitis in United States. (Proc. Pub. Bureau Anim. Indust., issued annually, 1935–1942.)
6. Meyer, K. F.: Summary of recent studies on equine encephalomyelitis, Ann. Int. Med. 6: 645–654, 1932.
7. Howitt, B. F.: Recovery of virus of equine encephalomyelitis from brain of child, Science 88: 455, 1938.
8. Fothergill, L. D., Dingle, J. H., Farber, S., and Connerly, M. L.: Human encephalitis caused by virus of eastern variety of equine encephalomyelitis, New Eng. J. Med. 219: 411, 1938.
9. Webster, L. T., and Wright, F. H.: Recovery of eastern equine encephalomyelitis virus

from brain tissue of human cases of encephalitis in Massachusetts, Science **88** : 305, 1938.

10. Rivers, T. M.: Viral and rickettsial infections of man, 1948, J. B. Lippincott Co., Philadelphia, p. 181.

11. Hammon, W. M.: Encephalitis in Yakima Valley, Washington: mixed St. Louis and Western equine types, J. A. M. A. **117** : 161–167, 1941.

12. Hammon, W. M., Reeves, W. C., Benner, S. R., and Brookman, B.: Human encephalitis in Yakima Valley, Washington, 1942, with forty-nine virus isolations (western equine and St. Louis types) from mosquitoes, J. A. M. A. **128** : 1133–1139, 1945.

13. Howitt, B. F.: Human encephalomyelitis and St. Louis encephalitis in California, 1939–1941, Am. J. Pub. Health **32** : 503–515, 1942.

14. Hammon, W. M., and Reeves, W. C.: Recent advances in epidemiology of anthropod-borne virus encephalitides, including certain exotic types, Am. J. Pub. Health **35** : 994–1004, 1945.

15. Richter, R. B.: Western equine encephalomyelitis occurring sporadically in a metropolitan area, J. A. M. A. **119** : 486–487, 1942.

16. Saphir, W., and Milzer, A.: Western equine encephalomyelitis in Chicago, J. A. M. A. **140** : 778–780, 1949.

17. Helwig, F. C.: Western equine encephalomyelitis following accidental inoculation with chick embryo virus: report of fatal human case with necropsy, J. A. M. A. **115** : 291–292 (July 27) 1940.

18. Gold, H., and Hampil, B.: Equine encephalomyelitis in laboratory technician with recovery, Ann. Int. Med. **16** : 556–559, 1942.

19. Hammon, W. M., Reeves, W. C., and Gray, M.: Mosquito vectors and inapparent animal reservoirs of St. Louis and Western equine encephalitis viruses, Am. J. Pub. Health **33** : 201–207, 1943.

20. Kitselman, C. H., and Grundman, A. W.: Equine encephalomyelitis virus isolated from naturally infected *Triatoma sanguisuga* Le Conte. Technical Bulletin 50, Kansas Agricultural Experiment Station, 1940, p. 1.

21. Syverton, J. T., and Berry, G. P.: An anthropod vector for equine encephalomyelitis, Western strain, Science **84** : 186–187, 1936.

22. Hammon, W. M., Reeves, W. C., Brookman, B., Izumi, E. M., and Gjullim, C. M.: Isolation of the viruses of Western equine and St. Louis encephalitis from *Culex tarsalis* mosquitoes, Science **94** : 328–330, 1941.

23. Sulkin, S. E.: Recovery of equine encephalitis virus (western type) from chicken mites, Science **101** : 381–383, 1945.

24. Reeves, W. C., Hammon, W. M., Furman, D. P., McClure, H. E., and Brookman, B.: Recovery of western equine encephalomyelitis virus from wild bird mites (*Liponyssus sylviarum*) in Kern County, California, Science **105** : 411, 1947.

25. Cox, H. R., Jellison, W. L., and Hughes, L. E.: Isolation of western equine encephalomyelitis virus from naturally infected prairie chicken, Pub. Health Rep. **56** : 1905, 1941.

26. McNutt, S. H., and Packer, A.: Isolation of western equine encephalomyelitis and hog-cholera viruses from supposedly hog-cholera immune swine, Vet. Med. **38** : 22–25, 1943.

27. Muckenfuss, R. S., Armstrong, C., and McCordock, H. A.: Encephalitis: Studies on experimental transmission, Pub. Health Rep. **48** : 1341–1343, 1933.

28. Meiklejohn, G., and Hammon, W. M.: Epidemic of encephalitis, predominantly St. Louis type, in Pinal County, Arizona, J. A. M. A. **118** : 961–964, 1942.

29. Howitt, B. F.: Human equine encephalomyelitis and St. Louis encephalitis in California, 1939–1941, Am. J. Pub. Health **32** : 503–515, 1942.

30. Bozalis, G. S., and Jones, A. B.: Epidemic encephalitis, St. Louis type: survey of outbreak, summer and fall of 1937, J. Oklahoma M. A. **31** : 164–171, 1938.

31. Ayres, J. C., and Feemster, R. F.: Public health aspects of the virus encephalitides, New England J. Med. **240** : 966–972, 1949.

"IMPROVEMENT" IN THE HYPERTENSIVE PAT-
TERN OF THE ELECTROCARDIOGRAM *

By Robert Sterling Palmer, M.D., F.A.C.P., *Boston, Massachusetts*

Changes in the electrocardiograms of patients with essential hypertension have been described and considered as: (1) Characteristic of that condition [1]; (2) Indicative of hypertensive heart disease [2]; (3) Objective criteria of progress either favorable or unfavorable as the result of drugs,[3] diet [4] or surgical treatment.[5]

Observations herewith presented show (a) that the hypertensive pattern may be reversed by weight loss without change in the blood pressure (figure 1); (b) that inverted T waves may be reversed in 16 days with a weight loss of only 11 pounds, left axis deviation and the hypertension continuing (figure 2), and (c) that apparent improvement in the hypertensive pattern may be promptly followed by a coronary thrombosis (figure 3).

CASE REPORTS

Case 1. A man of 45 with minimal organic changes and a strong family history of hypertension was nervously and physically fatigued and found to have an elevated blood pressure. For years he had struggled successfully in a very competitive business situation, and had been keenly aware of both personal feelings of handicap and an urgent need for success. During these same years he had been a hearty eater and heavy user of spirits. He was treated by sedatives, a rice diet, and a low sodium, low calorie diet varying according to his business travels. At times his blood pressure fell as low as 170 mm. Hg systolic and 110 mm. diastolic, but never to normal or near-normal levels. He lost 26 pounds in weight. The electrocardiogram (figure 1) showed reversal of the so-called hypertensive pattern, to wit, (a) upright instead of inverted T waves in Leads I, II, aVF, V$_5$ and V$_6$; (b) a more vertical instead of a tendency to left axis in Leads I, II and III, and (c) a low upright instead of a relatively high R in aVL.

The patient's clinical condition, including the blood pressure, has remained unchanged except for weight loss; his electrocardiogram, which formerly showed the hypertensive pattern, is now normal.

Case 2. A similar marked change in the T waves of Leads I, CF$_4$ and CF$_5$ occurred in 16 days in another patient treated by mild sedation and a low calorie (reduced fats), high protein and no added salt diet with a weight loss of only 11 pounds, the blood pressure though lower, remaining elevated. This patient had no complaints either before or after his weight loss (figure 2).

The change in T waves is quite definite, without significant alteration in axis. The weight loss was relatively small. There were no antecedent pain or any other symptoms or signs of coronary insufficiency.

Case 3. A 61 year old woman who had had hypertension for 15 years and a cerebral accident several years previously complained of typical anginal pain for six

years. After one month on a low fat, liberal protein, no added salt, low residue diet, and phenobarbital, 15 to 30 mg., and mannitol hexanitrate, 30 mg. four times daily, she was improved symptomatically, though the blood pressure remained about the same. The following changes in the electrocardiogram were noted in one month: An inverted T₁ became upright; an upright T₂ became inverted; an inverted T–CF₂ became upright; a diphasic T–CF₄ became upright; a deeply inverted T–CF₆ became
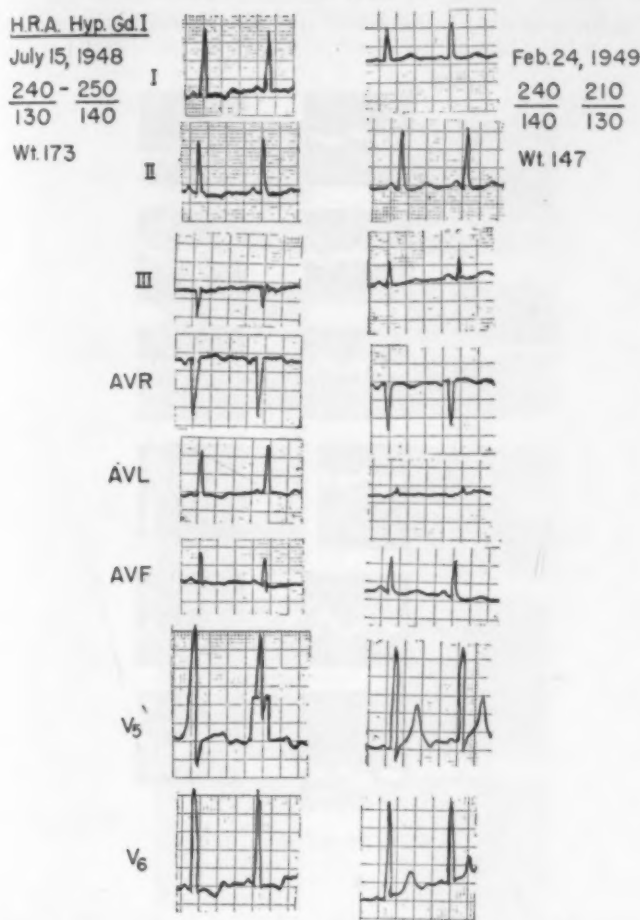

FIG. 1.   Reversal of the so-called pattern of left ventricular strain by weight loss, the clinical condition otherwise remaining the same.

upright (figure 3).   The next day she suffered a typical coronary infarction after an airplane flight to Florida.   Several months later her electrocardiogram showed the original pattern except for a "W" type QRS in Lead II and absent initial deflections in the precordial leads.   Her treatment, except for six weeks at bed rest, had remained the same.   Both the patient and her physician had been unduly encouraged by her symptomatic improvement and the seeming improvement in her electrocardiogram.

MISCELLANEOUS OBSERVATIONS

We have seen other instances sometimes less striking, of "improvement" in T waves associated with weight loss, the use of nitrates or other drugs, or for no assignable reason. In two patients following sympathectomy for hypertension there occurred improvement in the T wave pattern but a developing AV block. Also, we have seen improvement in the T waves prior to sympathectomy during weight loss in preparation for operation.
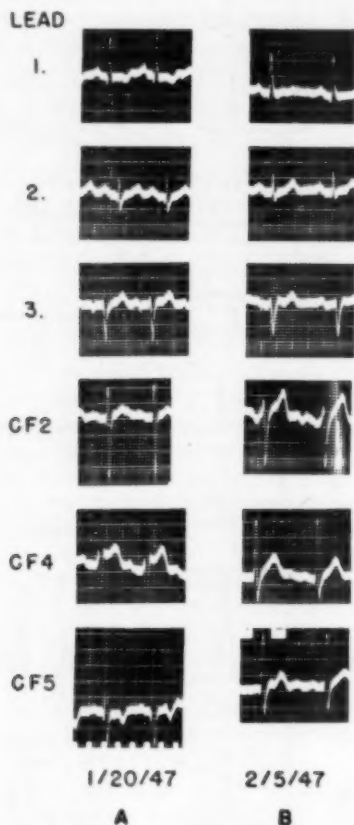

FIG. 2. "Improvement" in the "hypertensive pattern" in 16 days, with a weight loss of only 11 pounds, the electrical axis remaining the same.

Filley[6] found ST segment and T wave changes associated primarily with a high diastolic pressure, coronary sclerosis and hypertrophy of the heart as a whole, but not significantly related to a relative increased thickness of the left ventricular wall. In his study of 100 cases, the poor prognosis implied by these changes depended largely on other prognostic signs. The pattern of "left ventricular strain" was not in itself an indication that the myocardium had failed or was about to fail. Sensenbach[7] points out

that accepted standards of normality for the electrocardiogram are incorrect, since too many healthy young adults show changes which, according to these standards, are diagnostic of heart disease, and since many things cause these changes, including autonomic imbalance, neurocirculatory asthenia and anxiety. He lists 47 conditions, not primarily heart disease, which may be associated with these electrocardiographic changes.

Twenty-five years ago, in the beginning of clinical electrocardiography,[8] as now with unipolar electrocardiography,[9] the T wave which theoretically

LEAD

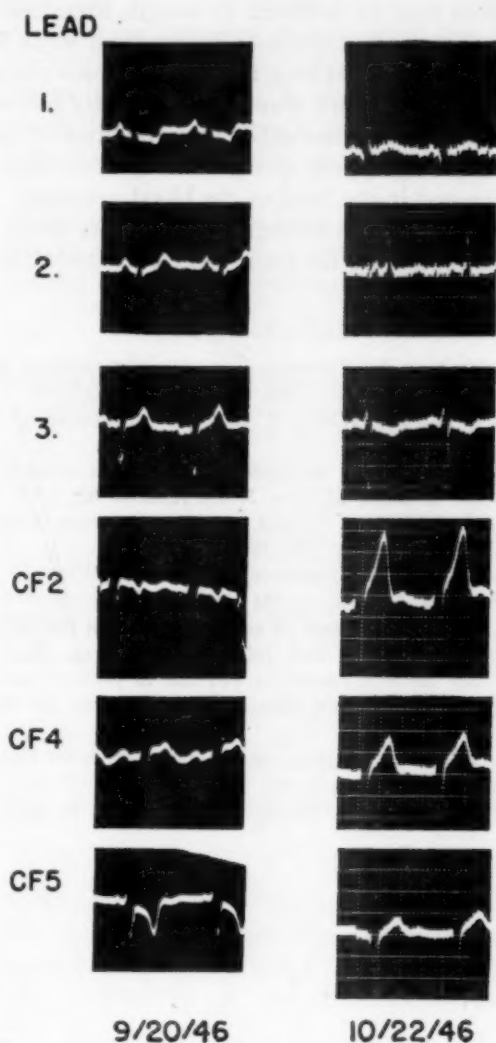1.

2.

3.

CF2

CF4

CF5

9/20/46   10/22/46

Fig. 3. Seemingly an improved electrocardiographic pattern in a patient with hypertension and coronary disease, followed within 24 hours by a typical coronary occlusion and myocardial infarction.

should be inverted after an upright initial ventricular complex was assumed
to be upright because the excitatory phase at the base was prolonged. Why
this should have been so is not known. In short, the precise nature of the
T wave is not known; as compared with the initial deflection of the ven-
tricular complex, it is unstable and is altered by many factors.

CONCLUSIONS

These observations suggest that the so-called hypertensive or left ven-
tricular strain pattern may be reversed by weight loss, other conditions re-
maining the same, that the pattern may be reversed in as little as 16 days
with comparatively slight weight loss, the electrical axis remaining the same,
that apparent signal improvement may be immediately followed by coronary
occlusion and infarction, and that other abnormalities of the electrocardio-
gram (as AV block) may appear along with apparent improvement in the
hypertensive pattern and in the level of the blood pressure.

It is submitted that electrocardiographic changes alone are not reliable
objective criteria in estimating the progress, either favorable or unfavorable,
in essential hypertension.

BIBLIOGRAPHY

1. Rykert, H. E., and Hepburn, J.: Electrocardiographic abnormalities characteristic of cer-
    tain cases of arterial hypertension, Am. Heart J. **10**: 942, 1935.
2. Evans, E., Mathews, M., and White, P. D.: The electrocardiogram in hypertension,
    Am. Heart J. **30**: 140, 1945.
3. Treis, E. D.: Recent advances in the medical treatment of essential hypertension with
    particular reference to drugs, M. Clin. North America **32**: 1247, 1948.
4. Kempner, W.: Some effects of the rice diet treatment of kidney disease and hypertension,
    Bull. New York Acad. Med. **22**: 358, 1946.
5. Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D.: Electrocardio-
    graphy in hypertension, J. A. M. A. **131**: 1476, 1946.
6. Filley, G. F.: The clinical significance of certain changes in the limb lead electrocardio-
    gram in essential hypertension, Bull. Johns Hopkins Hosp. **79**: 261 (Oct.) 1946.
7. Sensenbach, W.: Some common conditions, not due to primary heart disease, that may
    be associated with changes in the electrocardiogram, Ann. Int. Med. **25**: 632 (Oct.)
    1946.
8. Lewis, T.: The mechanism and graphic registration of the heart beat, Ed. 3, 1925, Shaw
    and Sons, London, p. 120 et seq.
9. Goldberger, E.: Unipolar electrocardiography, 1947, Lea & Febiger, Philadelphia, p. 47.

THERAPY OF SUBACUTE ENTEROCOCCUS
(*STREPTOCOCCUS FECALIS*)
ENDOCARDITIS *

By LEO LOEWE, M.D., SAMUEL CANDEL, M.D., F.A.C.P., and HAROLD B.
EIBER, M.D., *Brooklyn, N. Y.*

DESPITE the uniformly favorable results following the use of antibiotics
in the therapy of subacute bacterial endocarditis due to *Streptococcus
viridans*,[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] the same treatment programs
when the enterococcus (*Streptococcus fecalis*) is the offending organism
have mostly met with failure. Although an occasional success has been
reported,[19, 20, 21, 22] the therapy of enterococcus endocarditis still remains a
challenge.

The purpose of this communication is to analyze the factors responsible
for the failures and to describe methods which have been adopted in an
effort to overcome the obstacles encountered in treating this refractory
disease.

TABLE I

Classification of Infecting Organisms in 157 Cases of Subacute Bacterial Endocarditis

Type	No. of Cases	In Vitro Penicillin Sensitivity—O.U./ml. Test Broth			
		Bacteriostasis		M.L.D.	
		Range	Average	Range	Average
Streptococcus viridans					
Streptococcus sanguis (s.b.e.)	85	.004–.25	.08	.008–2.0	.52
Streptococcus mitis	23	.008–.25	.07	.06–1.0	.38
Streptococcus bovis	13	.03–.25	.09	.03–2.0	.51
Streptococcus salivarius	1	.25		.25	
Not subtyped	17	.008–1.0	.14	.03–2.0	.36
Staphylococcus aureus	7	.03–12.5	3.9	.06–25.0	12.4
Enterococcus	6	3.2–6.3	4.6	12.5–25.0	22.9
Erysipelothrix rhusiopathiae	1	.03		.06	
Candida Krusei	1	Insensitive			
Pneumococcus—Type 33	1	Sensitive			
Spirochaeta vincenti	1	Sensitive			
Veillonella gazogenes	1	10.0		30.0	

Since the introduction of antibiotic therapy, 157 patients with subacute
bacterial endocarditis due to known infective organisms have been treated
at the Jewish Hospital of Brooklyn (table 1). As may be noted from this
tabulation, six of the 157 patients (3.8 per cent) were infected with entero-
cocci.

TABLE II

Clinical Data—Six Cases of Subacute Enterococcus Endocarditis

Case No.	Name	Age	Sex	Date of Admission	Primary Cardiac Condition	Results	Remarks
1	D. C.	61	M	4-6-45	None	Treatment failure	Origin of infection—urologic procedure. Terminal cerebral embolus. Died 4 weeks after admission.
2	W. D. M.	57	M	1-12-46	Chronic rheumatic valvular heart disease—aortic	Treatment failure	Portal of entry—fistula-in-ano, rectal abscess. Thrombophlebitis. Died 15 days after admission.
3	V. D. C.	27	F	1-24-46	Chronic rheumatic valvular heart disease—aortic and mitral	Treatment failure	No therapy for 6 months, followed by 3 months of unsuccessful treatment prior to admission. Died despite massive combined therapy.
4	S. S.	49	M	3-1-46	Chronic rheumatic valvular heart disease—mitral	Recovered	Arrestive therapy prior to admission. Successful response to massive penicillin therapy with PAH* for enhancing purposes. Short span of streptomycin. Intense drug sensitivity. Discharged cured after 163 hospital days.
5	F. B. R.	63	M	5-29-47	Chronic rheumatic valvular heart disease—aortic and mitral	Treatment failure	Subcurative therapy for 5 months prior to admission. Unfavorable response to penicillin in adequate dosage. In vitro organism resistance to streptomycin prohibited clinical use of this drug.
6	B. B.	55	M	12-12-47	None	Recovered	No antecedent cardiac lesion. Source of infection—urologic procedure. Severe cutaneous and renal toxic reaction to streptomycin. Drug sensitivity corrected by procaine intravenously. Satisfactory response to curative penicillin schedules. Thromboembolism successfully treated with heparin/Pitkin Menstruum.

* PAH—Sodium para-aminohippurate for enhancing penicillin levels.

These six patients (table 2) have been the medium whereby a rational therapeutic approach to this disease has been evolved. A brief review of these six case histories follows, with an analysis of the problems which they presented:

CASE REPORTS

Case 1. A 61 year old male junk dealer was admitted to the Mayo Clinic, November 20, 1944, for a lower urinary tract obstruction. A transurethral resection was done for an hypertrophied prostate. Six days postoperatively he had a chill and fever. The blood culture was positive for *Staphylococcus aureus*. Under penicillin therapy, the urinary tract infection subsided and the blood culture became negative.

On February 19, 1945, the patient returned to the Mayo Clinic with evidence of a general infection. A systolic and diastolic murmur was heard over the aortic area. The blood culture was now positive for enterococcus. He was hospitalized February 28 and received treatment until March 20, 1945. Because of the persistence of low, irregular fever and positive blood cultures, he was discharged with a diagnosis of active subacute enterococcal endocarditis. The prognosis was considered hopeless.

On April 6, 1945, he was admitted to the Jewish Hospital because of the continued fever. In addition to the history mentioned above, he stated that he had been treated

for ulcer of the stomach 25 years previously. Up to the present illness he had never been aware of any cardiac lesion, nor did he have any cardiac symptoms.

Physical examination disclosed a well-nourished and well-developed adult male in no acute distress. The blood pressure was 110 mm. Hg systolic and 60 mm. diastolic, temperature 101° F., pulse 110 and regular, and respirations 24. All findings were negative except for the heart, which exhibited a double aortic murmur transmitted to the apical region. The legs showed a 2 plus pitting edema.

Laboratory studies were as follows: Blood culture revealed 96 colonies of enterococcus per ml. of blood. The blood count was hemoglobin 57 per cent, erythrocytes 3.11 million, and leukocytes 13,000 per cu. mm., with polymorphonuclears 85 per cent, lymphocytes 14 per cent, monocytes 1 per cent. The urinalysis showed sp. gr. 1.014, albumin very faint trace, occasional red blood cell and white blood cell. The blood urea nitrogen, 15.9 mg. per cent; the total protein 5.99 gm., albumin 3.39 gm., globulin 2.60 gm., and A/G ratio 1.3. The erythrocyte sedimentation rate was 100 mm. hr. (Westergren).

TABLE III

Treatment Statistics—Six Cases of Subacute Enterococcus Endocarditis

Case No.	Duration of Disease Weeks	Previous Penicillin Therapy	Treatment Program						Other Drugs	Results
			Penicillin Therapy			Streptomycin Therapy				
			Span Weeks	Daily Dose	Total Dose	Span Weeks	Daily Dose	Total Dose		
				Million O.U.			Micrograms			
1	20	Yes	3*	5–10	167					Died
2	8	Yes	2	20	280	2	1.5	21		Died
3	36	Yes	50	5–40	3,799	3	2	42	Sulfa bacteriophage	Died
4	8	Yes	10	5–30	2,040	1	2	14	Sulfa PAH* sod. salicylate	Rec.
5	28	Yes	8	10–20	780					Died
6	7	No	3	10	200	3	1–2	40	Intravenous procaine	Rec.

* PAH—Sodium para-aminohippurate for enhancing penicillin blood levels.

Roentgenogram of the chest showed both lungs clear except for exaggerated basal markings suggesting a degree of bronchial and peribronchial infiltration. The heart did not appear enlarged.

Penicillin * therapy was promptly instituted, a total of 167 million units being given over a 23 day period (table 3). The patient received four blood transfusions of 500 ml. each.

Clinical Course: During the first week the temperature ranged from 100° to 102.2° F.; the second week it ranged from 99° to 100.2° F. Two weeks after admission the patient had a sudden episode of precordial and epigastric pain. He became cold and clammy and the blood pressure fell to 80 mm. Hg systolic and 32 mm. diastolic. The heart sounds were distant and rapid and there were numerous râles throughout the chest. The next day he had a sudden convulsive seizure and developed a left hemiplegia. The temperature rose to 104° F., pulse 140, respirations 30 to 45. He continued to fail, and died May 3, 1945.

COMMENT

This enterococcus infection followed urinary tract manipulation. The adverse outcome in this case was attributable to the continued use of a sub-curative treatment program. At no time was the infection under control due to inadequate dosage schedules. The latter can be ascribed in part to limited supplies of penicillin and to the nonexistence of practical enhancing agents. The sudden cerebral embolization and terminal lobar pneumonia which caused exitus were episodes in a progressive disease.

Case 2. A 57 year old male architect was admitted with fever and weakness of two months' duration on January 12, 1946. He had a history of rheumatic fever in childhood. At 28 years of age he was rejected for military service because of his cardiac condition.

A little more than two months before the onset of the present illness he had received a series of colonic irrigations. Following these, he began to complain of weakness and noted a low grade fever.

He was hospitalized in Pittsburgh, where a diagnosis of subacute bacterial endocarditis was made. During his hospital stay a rectal abscess was drained. The enterococcus was cultured from the blood. He received 17 million units of penicillin intramuscularly over a period of four weeks. However, his condition rapidly became worse and he was then transferred to the Jewish Hospital in Brooklyn for intensive therapy.

On admission, physical examination revealed an almost moribund 57 year old man. The sensorium was cloudy. The blood pressure was 130 mm. Hg systolic and 30 mm. diastolic, temperature 103° F., pulse 130, and respirations 28. There were numerous petechiae in the region of the left shoulder. The lungs were resonant and there were many inspiratory râles at both bases. The heart percussed within normal limits and there was a loud systolic-diastolic murmur over the aortic area and audible at the apex. The abdomen was soft. The liver was not felt but the spleen was easily palpable. The extremities showed no edema. Rectal examination disclosed a fistula-in-ano with evidence of abscess formation.

The laboratory studies were as follows: Blood culture showed innumerable colonies of an enterococcus which was completely inhibited by 25 O.U. of penicillin and by 250 micrograms of streptomycin per ml. of test broth (table 4).* The blood sugar was 119 mg. per cent, urea nitrogen 26.5 mg. per cent. The blood count was hemoglobin 70 per cent, erythrocytes 3.55 million, leukocytes 12,000 per cu. mm., with polymorphonuclears 83 per cent, band forms 4 per cent, lymphocytes 11 per cent and monocytes 2 per cent. The urinalysis showed sp. gr. 1.020, albumin, faint trace, red blood cells 5 to 10 per high power field. The erythrocyte sedimentation rate was 45 mm./hr. (Westergren). The electrocardiogram disclosed severe myocardial damage.

Therapy was initiated with 20 million O.U. of penicillin intravenously daily and continued for 14 days; the total penicillin administered was 280 million O.U. (table 3). In addition, streptomycin, 1.5 gm. intramuscularly, was given daily for 14 days. He also received two blood transfusions.

On the eleventh day of hospitalization his condition was still grave. He began to show evidence of thrombophlebitis of the right leg and was placed on anticoagulation therapy with heparin/Pitkin Menstruum.[23] He developed decubitus ulcers of the heels of both feet. The blood culture was sterile on the ninth day, although the fever persisted.

* In in vitro sensitivity tests employed were those described by Rosenblatt, Alture-Werber, Kashdan and Loewe for penicillin [23] and by Alture-Werber and Loewe for streptomycin.[24]

On the thirteenth day following the intravenous administration of plasma he became dyspneic and had an episode of syncope. He was given digitalis but the dyspnea and cyanosis increased. He died on the fifteenth day.

Significant Necropsy Findings.†

Gross. Heart and Aorta: The heart weighed 480 gm. and measured 12.6 cm. from apex to base and 11.2 cm. across the base. The apex was made up of the left ventricle. The epicardium was slightly roughened and showed a thin fibrinous exudate. There was a firmly adherent thrombus in the left auricular appendage. The myocardium gave a thrush-breast appearance and, on section, many areas of darker red were seen in the myocardium, indicating areas of softening. The coronary vessels were patent and somewhat sclerotic throughout. The chordae tendineae were thin and delicate in both sides of the heart. The aortic valve showed several large, firmly adherent pink-red vegetations in its cusps. These vegetations measured up to 1 cm. in diameter and were pink and homogeneous on cut section. The valve cusps themselves were opaque and the anterior cusp was perforated. The commissures were fused. The mitral valve cusp was more vascular than normal but no vegetations were seen on the mitral leaflets. The endocardium was smooth and glistening except below the aortic valve, where small vegetations were seen, and the lining of the aorta was sclerotic.

TABLE IV

Subacute Enterococcus Endocarditis, Comparison of in vitro Sensitivity and Blood Levels

Case	In vitro Sensitivity				Penicillin				Results
	Penicillin (O.U./ml. test broth)		Streptomycin (micrograms/ml.)		Daily Dose million O.U.	Blood Levels (O.U./ml.)			
	Bacteriostasis	M.L.D.	Bacteriostasis	M.L.D.		Low	High	Aver.	
1.D. C.	3.2	25.0	125	250	5	4	30	12	Dead
2.W. M.	6.3	25.0	62	250	20	24	60	35	Dead
3.V. D.	3.2	25.0	62	125	20	20	60	32	Dead
4.S. S.	6.3	25.0	62	250	40	17	90	47	Recovered
5.F. B. R.	3.2	12.5	31	250	20	16	150	94	Dead
6.B. B.	6.3	25.0	31	62	25	40			Recovered

Respiratory System: There were firm fibrous adhesions of both lungs to the diaphragm.

Gastrointestinal Tract: There was a fistula-in-ano.

Liver and Biliary System: Liver was enlarged and, on section, showed increased lobular markings and marked congestion.

Kidneys: The external surface of the right kidney exhibited many depressed white scars and other pale gray areas. The capsule stripped with ease except over the scarred areas. On section, the cortex was clearly differentiated from the medulla and wedge-shaped; gray-white areas were clearly seen. The entire capsule of the left kidney stripped with difficulty and, on section, was similar to the right kidney.

Spleen: The spleen weighed 420 gm. At both poles were areas of gray pink which were sharply circumscribed and measured 8.9 by 8.2 cm. in diameter. They were cystic in consistency. The rest of the spleen was moderately soft in consistency.

Microscopic Notes.

Heart and Aorta: In a preparation from the wall of the aorta the wall was seen

to be fragmented, and there were many clear spaces noted in the intima. Very few nuclei were seen, and there was some infiltration with round mononuclear cells. The elastic lamina was not seen. The vegetation was made up of homogeneous pink-staining material, with several collections of light blue-staining masses scattered throughout. Some of these were areas of calcification and others were bacterial in nature.

In a preparation from the aortic valve stained with hematoxylin and eosin, the valve was hyalinized and pink-staining. No cellular structures and no nuclei were seen in most of the valve. There are some areas that showed clear spaces with swollen and fragmented nuclei. In other regions there were round light blue-staining areas, bacterial in nature. The vegetation was homogeneous pink and light blue, with small dark blue areas scattered throughout. There were some areas in the vegetation that showed clear spaces and pyknotic nuclei.

In a preparation from the aortic valve stained with Gram's stain, there were large blue-staining clumps of bacteria seen throughout the slide.

In a preparation from the aortic valve stained with elastic van Gieson's stain, the dark blue-staining lines of elastic tissue were seen to be very sparse. The red-staining collagenous tissue was abundant, as was the yellow-staining muscle tissue.

In a preparation from another portion of the aortic valve stained with hematoxylin and eosin, the vegetation was seen to be intimately adherent, and the valve and the valvular tissue showed more of a cellular nature than did the other slides. The vegetation was similar to that seen on other sections.

In a preparation from the left ventricular wall, the epicardium was increased in thickness and infiltrated with a few mononuclear round cells. The subepicardial fat was increased in amount. The myocardial bundles were hypertrophied, as were the myocardial fibers. In a preparation from the interventricular septum, essentially the same picture was seen.

In a preparation from the mitral valve, a vegetation was seen on the proximal portion of the valve. The vegetation was blue-staining, fragmented and infiltrated with polymorphonuclear cells. The surface of the valve opposite the vegetation was infiltrated with mononuclear round cells. The distal portion of the valve was infiltrated with round cells and showed deposits of pink-staining hyalin material and some fibrous tissue proliferation.

Lung: In a preparation from the right lung, the pleura was increased in thickness by fibrous connective tissue. The pleural surface showed fibrous tissue tags. Many of the alveoli were filled with pink-staining fluid and some round mononuclear cells. The blood vessels were markedly distended.

In a preparation from the left lung, the pleura was also thickened, and essentially the same pathology was seen as in the right lung except that there were fewer alveoli containing fluid and cells.

Liver: In a preparation from the liver, the lobular architecture was fairly well maintained. The liver cells were broad. The cytoplasm was granular and the cell borders were indistinct. The cytoplasm of these cells was vacuolated, the nuclei were pyknotic, and there were focal areas of fatty changes. The periportal connective tissue was somewhat increased in amount.

Kidney: In a preparation from the right kidney, a large area showed necrosis of all cells, staining homogeneous pink in color. No cellular structure was seen except that of infiltrated mononuclear round cells and polymorphonuclear cells. In other areas the glomeruli were numerous and large and unevenly distributed throughout the kidney. The intraglomerular capillary loops were distended with blood, as were the afferent arterioles. The subcapsular spaces were very narrow and almost obliterated in some Malpighian bodies. The tufts were surrounded by delicate connective tissue. The epithelium of the convoluted tubules was high cuboidal, the cyto-

plasm was granular, the cell borders were not clearly seen, and the nuclei were round and dark-staining. The lumina were wide and contained collections of granular pink-staining material. The epithelium of Henle's loops and collecting tubules were well preserved, and some of the lumina contained pink-staining hyaline casts. There was a normal amount of connective tissue separating the tubules. The capillaries were congested. One of the large blood vessels near the necrotic area contained an organized and canalized old thrombus.

A preparation from the left kidney showed similar changes.

Spleen: In a preparation from the spleen, the capsule was somewhat thickened and hyalinized. The trabeculae were not conspicuous. The cytoarchitecture was badly distorted and only a few Malpighian corpuscles were seen. No germinal centers were seen. Many of the vessels were markedly congested, and there was a great deal of hemorrhage in one area of the preparation. The sinuses were filled with red blood cells and lined by endothelial cells containing small granules of black and brown pigment. A large area of this preparation was homogeneous pink- and blue-staining, without much cellular structure. Very few nuclei were seen and these were pyknotic. There was some infiltration of mononuclear and polymorphonuclear cells in this area.

COMMENT

This case was a 57 year old male who previously had been given relatively insignificant amounts of antibiotics for four weeks, during which time his general condition deteriorated so rapidly that he was admitted to our institution in a moribund, comatose condition. The portal of entry for the enterococcus was probably the abscess complicating the fistula-in-ano. An intensive, combined treatment program was instituted promptly and was apparently adequate, as judged by blood levels (table 4) and by the fact that the blood stream was sterilized. However, the tissue damage was so extensive and irreversible that the patient did not survive to receive the benefits of prolonged therapy.

Case 3. A 27 year old Puerto Rican woman was admitted to the Jewish Hospital on January 24, 1946, with a history of fever for nine months. She had received little or no treatment for about six months, following which she was admitted to the Mt. Sinai Hospital, New York. Nine weeks prior to admission to that institution she had had fever of 102° F., weakness, chest pain, tachycardia, dyspnea, orthopnea and swelling of both feet. At Mt. Sinai Hospital she was diagnosed as having subacute bacterial endocarditis and was vigorously and seemingly successfully treated for a period of three months. After discharge the fever promptly recurred and she was referred to the Jewish Hospital.

Physical examination revealed a thin young Puerto Rican female who looked chronically ill. Her blood pressure was 98 mm. Hg systolic and 60 mm. diastolic, temperature 98.6° F., pulse 110, and respirations 28. The head and neck were normal. The apex beat of the heart was in the seventh interspace outside the nipple line. There were systolic and diastolic murmurs over the aortic area. There was a soft diastolic murmur at the apex. A loud rough systolic apical murmur was transmitted to the left axilla. There was dullness at the right base posteriorly where the breath sounds were absent. A few râles were audible at the left base. The liver edge was felt down to the umbilicus. The edge of the spleen was palpable. The extremities showed a 2 plus pitting edema. There was marked clubbing of the fingers. No petechiae were seen.

Blood culture disclosed a hemolytic streptococcus, 105 colonies per ml. of blood, which typed out as an enterococcus. The M.L.D.* values were 25 O.U. and 125 micrograms per ml. of test broth for penicillin and streptomycin, respectively (table 4). On admission the blood count was hemoglobin 74 per cent, erythrocytes 3.8 million and leukocytes 16,050 per ml., with polymorphonuclears 79 per cent, band forms 4 per cent, lymphocytes 11 per cent, monocytes 3 per cent and eosinophils 3 per cent. Blood urea nitrogen was 11.5 mg. per cent. The urinalysis showed sp. gr. 1.018, albumin very faint trace, and red blood cells, 20 to 30. The erythrocyte sedimentation rate was 11 mm./hr. (Westergren).

Roentgenogram of the chest demonstrated a pneumonitis at the right base and cardiac enlargement, particularly of the left ventricle.

The clinical diagnosis was subacute bacterial endocarditis, chronic rheumatic valvular disease, aortic and mitral stenosis and regurgitation, and congestive heart failure.

The patient was digitalized and treated for heart failure. Penicillin therapy was begun, with 5 million units daily for one week, followed by 10 million units for the next two weeks, and then 20 million units daily for 51 days (table 3). All the penicillin therapy was given intravenously, with 100 mg. of heparin daily incorporated in the venoclysis.

The temperature returned to normal on the tenth day and remained so for the next 84 days. A penicillin level of 30 Oxford units (table 4) was attained on the twenty-sixth day, with 20 million units of penicillin daily, given intravenously. The blood became sterile on the twelfth day and remained so until discharge. Therapy was discontinued on the seventy-third hospital day and the patient discharged on the ninety-fourth day (April 27, 1946).

Second Admission: Six days later there was recurrence of fever. The patient was readmitted to the hospital May 2, 1946. A blood culture done the next day showed 103 colonies of enterococcus per ml. of blood. She was given 20 million units of penicillin and 100 mg. heparin daily for 15 days. The temperature subsided on the third day of admission. The dosage of penicillin was increased to 30 million units daily for the next 10 days. The patient's clinical condition was satisfactory. The penicillin therapy was interrupted for one week, during which time 2 gm. of streptomycin and 6 gm. of sulfadiazine were given daily.

Another course of penicillin was administered immediately thereafter. Thirty to 40 million units of penicillin were given daily for 18 days. This was again followed by 2 gm. of streptomycin daily for eight days. Then 40 million units of penicillin were given daily for 14 days. At this time (ninety-fourth day) there was a temperature elevation to 102° F. for seven days. On the ninety-seventh day, 41 colonies of enterococcus per ml. of blood were recovered for the first time since the admission blood cultures.

Streptomycin therapy was resumed for two weeks. There was an excellent response as far as the fever and the patient's subjective symptoms were concerned for one and one-half weeks. Another elevation of temperature occurred, and 55 colonies of enterococci per ml. of blood were again recovered.

On the one hundred twentieth day, when fever still persisted, a combination of penicillin and bacteriophage therapy was instituted. There was again a prompt disappearance of temperature which lasted for one week, until it rose to around 100° F. and barely reached 101° F. for the next five weeks. The phage was discontinued. In 48 hours the temperature increased, and 10 days later bacteriophage and penicillin

---

* In the clinical correlation of in vitro antibiotic sensitivity tests,[26, 27] we realized the importance of determining the minimal lethal dose (M.L.D.) for the infecting organism in addition to the usual bacteriostatic end point. We accordingly modified our assays and have come to rely primarily on the M.L.D. values for establishing the treatment program.

were again given. However, the fever persisted for the next nine weeks, in spite of massive therapy with penicillin, streptomycin and bacteriophage. Blood cultures were regularly positive. For the four weeks which followed, until discharge, the patient ran a septic course, with fever ranging from 99° to 103° F. She was discharged as a treatment failure 258 days after her second admission, despite 1,145 million units of penicillin during the first admission and 2,654 million units during the second admission. This made an overall total of 3,799 million units of penicillin, in addition to 42 gm. of streptomycin and 3,190 ml. of bacteriophage.

COMMENT

This 27 year old Puerto Rican female was undiagnosed for six months, following which she was intensively treated for three months. This span of therapy evidently failed to terminate the infection and she was referred for further treatment. This case was a treatment failure despite prolonged, intensive, heroic therapy. This experience reaffirms the fact that this disease must be recognized promptly, so that the patient may receive the benefits of adequate therapy at the earliest possible moment. Only in this manner can widespread invasion with the development of invulnerable, encapsulated lethal lesions be prevented.

Case 4. A 49 year old male tailor was admitted to the Jewish Hospital March 1, 1946.

At the age of 39 years he had been told for the first time that he had a cardiac condition. He had had no symptoms referable to his heart at any time before admission.

Two months before admission he had a sudden episode of malaise with high fever. He was seen at home by his physician, who put him on "sulfa" therapy. At the end of a week he got out of bed, only to have a recurrence of fever. A blood culture was done and bacteria were found. He was given 62 million units of penicillin over a seven week period, despite which his fever persisted. He was then hospitalized for further therapy.

On physical examination the blood pressure was 112 mm. Hg systolic and 60 mm. diastolic, temperature 100.4° F., pulse 90, and respirations 20. No petechiae were found. The teeth showed evidence of considerable dental repair. The lungs were clear. The heart was not enlarged to percussion and its rhythm was regular. At the apex the first heart sound had a slapping quality; a diastolic murmur was audible at the apex and was transmitted to the left axilla. P₂ equalled A₂.

The liver was enlarged two fingerbreadths and the spleen was palpable two fingerbreadths below the costal cage. The extremities were negative. The admission diagnoses were: (1) chronic rheumatic valvular heart disease, mitral stenosis, normal sinus rhythm, early right heart failure; (2) subacute bacterial endocarditis.

Blood cultures revealed the enterococcus. The M.L.D. values were 25 O.U. and 250 micrograms per ml. of test broth for penicillin and streptomycin, respectively (table 4).

The patient was given a course of treatment during which he received 44 million O.U. of penicillin over an eight day period. This was given in conjunction with sodium para-aminohippurate [28] * and heparin. The dose was then increased to 20 million O.U. daily for another 11 days. The spleen was no longer palpable, but the

* The authors are indebted to the Medical Research Division, Sharp & Dohme, Inc., for the generous supplies of sodium para-aminohippurate and Staticin (caronamide) used in these studies.

patient developed urticaria and maculopapular eruption. Because of the persistence of a septic type of temperature, the penicillin dosage was increased to 30 million units daily without sodium para-aminohippurate but with the addition of 2 gm. of streptomycin intramuscularly daily (table 3).

The general condition of the patient improved but the temperature was still septic and ranged from 99.2° to 104° F. The maculopapular eruption persisted. After seven days the streptomycin was discontinued, since it apparently exerted no additional beneficial effect. On the eleventh day after the 30 million unit dosage was started, the patient developed swollen, red-hot wrist joints, and he was placed on salicylates for five days. There was no response of joints or temperature to the salicylates. Sulfadiazine was started, 1 gm. every four hours in conjunction with the massive penicillin therapy. The septic temperature regressed slowly and varied from 99° to 102° F. All therapy was discontinued after the blood cultures had been sterile for four weeks. Two weeks after cessation of therapy the temperature receded and the maculopapular eruption started to fade. The patient was out of bed four weeks after treatment had been discontinued. The blood cultures remained sterile. One week later there was a recurrence of the maculopapular eruption and the temperature rose to 101° F. When he was given sodium salicylate, the fever subsided in 24 hours and the rash disappeared. He was discharged as cured on the one hundred sixty-third hospital day and has remained well to date, a period of over two years.

COMMENT

This 49 year old male with chronic rheumatic heart disease was diagnosed promptly and treated with intensive though subcurative doses of penicillin for two months, which, however, prevented marked deterioration. His cardiovalvular apparatus was thereby spared and remained relatively intact so that he was able to withstand the prolonged exacting therapy necessary to effectuate an excellent recovery. There was no discernible portal of entry. His treatment was complicated by a skin eruption and arthritis, both of which were probably drug sensitization phenomena. The persistent temperature, not unusual with massive antibiotic therapy, confused the clinical picture but promptly subsided with suspension of all therapy. A significant feature of this case is the relative freedom from sequelae following the infection.

Case 5. A 63 year old Canadian male was admitted to the Jewish Hospital of Brooklyn, May 29, 1947, with a history of fever and weakness of six months' duration. He had had pneumonia at 23 years of age. There was no history of rheumatic fever or allied conditions.

In November, 1946, he began to have daily afternoon rises of temperature to 103° F. and complained of malaise and anorexia. He was hospitalized in Canada on December 31, 1946, where a diagnosis of endocarditis was made. For this he received penicillin injections every five hours, and after six weeks of therapy he was discharged as cured.

There was prompt recurrence of fever three days after discharge. He was rehospitalized and penicillin treatment was resumed, following which the blood cultures became negative. However, when the blood cultures became positive again, the patient became discouraged and left the hospital in Canada against advice.

The examination on admission to the Jewish Hospital revealed an elderly white male who appeared older than his stated age. The blood pressure was 120 mm. Hg systolic and 68 mm. diastolic, temperature 100° F., pulse 100, and respirations 20.

The eyes, ears, nose and throat were essentially negative. He appeared edematous. The heart percussed within normal limits, and there was a harsh presystolic apical murmur which was transmitted towards the left axilla. There was also a systolic apical murmur. A harsh diastolic murmur was audible over the aortic and tricuspid areas. The lungs were normal.

The abdomen was soft; no abnormal masses or organs were palpable. Several petechiae were observed on the abdominal wall. The extremities were negative except for many petechiae over the left tibia.

The admission diagnosis was subacute bacterial endocarditis, chronic rheumatic valvular heart disease (compensated), aortic insufficiency, mitral regurgitation and stenosis, regular sinus rhythm.

The blood culture taken on May 29 was reported as containing enterococci, 132 colonies per ml. of blood. The M.L.D. values were 12.5 O.U. and 250 micrograms per ml. of test broth for penicillin and streptomycin, respectively (table 4). The hemoglobin was 47 per cent and erythrocytes 2.5 million per cu. mm. The urine: sp. gr. 1.010, albumin, faint trace, and red blood cells 2 to 3 per high power field. The erythrocyte sedimentation rate was 87 mm./hr. (Westergren).

On admission the treatment program consisted tentatively of 10 million units of penicillin daily by vein with heparin. This was continued for two weeks until the enterococcus was fully processed, whereupon the dosage was raised to 20 million units daily; patient received a total of 780 million Oxford Units (table 3). The in vitro values for streptomycin were so high that the dosages required to attain therapeutic levels were in the toxic range, especially for long term therapy. Its clinical use was therefore abandoned.

The fever never exceeded 102.6° F. during the first week, when it fell by lysis. During the second week the temperature hovered around 100° F. It dropped below 100° F. after the twenty-third day, when the blood culture became sterile, and remained so until discharge.

He received four transfusions, following which his hemoglobin rose to 70 per cent. On the fortieth day he had a chill and temperature of 104° F. This recurred on the forty-seventh and forty-ninth days. For the succeeding week the temperature remained around 100° F. and then dropped to below 100° F. The blood cultures were negative.

The patient was discharged, much improved clinically, on the sixty-sixth day, with the knowledge, however, that not enough time had elapsed to ascertain whether the infection had been completely eradicated. Subsequent events proved that the infection had not in fact been terminated. He returned to Canada, where he died shortly thereafter.

COMMENT

This case, a 63 year old Canadian male, was a treatment defeat. For a span of six months prior to admission to our institution he had received inadequate dosages of penicillin. This prolonged period of subcurative therapy might well have permitted the development of encapsulated, invulnerable and possibly calcified lesions, which were probably responsible for the unfavorable response to suitable therapy. When it was discovered that he was infected with the enterococcus he was promptly given intensified antibiotic dosage commensurate with the in vitro data. Here again, the necessity for early diagnosis and prompt, adequate therapy was manifest. No portal of entry could be elicited.

Case 6. A 55 year old male theatrical agent was admitted to the Jewish Hospital, December 12, 1947, for fatigability, difficulty in concentration, and unprovoked episodes of weeping of seven weeks' duration.

He gave a history of a penile lesion in 1915 which was possibly luetic. Ten months before this admission he had been treated for an impassable urethral stricture. Intravenous urography showed normal kidneys which excreted well. He underwent urethral dilatation under anesthesia, and an indwelling catheter was introduced. Culture of the urine revealed *B. coli.*

His urinary symptoms abated following the operative procedure. He remained well until seven weeks before admission, when symptoms of tiredness, difficulty in concentration and increased emotionalism developed. Four weeks before admission he noted exertional dyspnea. At this time a heart murmur was noted for the first time.

Physical examination revealed a well nourished and well developed adult male, slightly dyspneic. The blood pressure was 155 mm. Hg systolic and 90 mm. diastolic, temperature 98.6° F., pulse 90, and respirations 20. There were a few fine crepitant râles at both bases. The heart showed an apical systolic murmur. The liver was enlarged to five fingerbreadths below the costal cage. The lower extremities showed a 2 plus pitting edema.

Four consecutive blood cultures disclosed enterococci in abundance. The penicillin M.L.D. sensitivity was reported as 25 O.U., and streptomycin as 62 micrograms per ml. of test broth (table 4). The enterococcus was also cultured from the urine. The hemoglobin was 43 per cent, erythrocytes 2 million, leukocytes 7,700 per cu. mm., with polymorphonuclears 68 per cent, band forms 14 per cent, and lymphocytes 20 per cent. Blood urea nitrogen was 33.8 mg. per cent. The total protein was 5.5 gm., with 2.5 gm. of albumin and 3.0 gm. of globulin; the A/G ratio was 0.8. The blood Kline test was 2 plus (doubtful), and the Kahn and Wassermann tests were negative. Urinalysis showed sp. gr. 1.005, albumin 2 plus, and numerous red and white blood cells. A urine concentration test showed fixation of specific gravity, with no specimen over 1.010. The erythrocyte sedimentation rate was 100 mm./hr. (Westergren).

The clinical diagnosis was subacute bacterial endocarditis, mitral stenosis and regurgitation with congestive heart failure, and chronic pyelonephritis.

During the first hospital week, the temperature varied from 100° F. to 103° F.

He was digitalized, given mercurial diuretics, and put on a salt-poor diet. He was transfused with whole blood. Because of the favorable streptomycin in vitro values, therapy was started with 2.0 gm. of streptomycin daily, which was given for 17 days, followed by 1 gm. daily for six days (table 3). Despite this therapy, he remained febrile and the congestive heart failure persisted. He developed a severe dermatitis with exfoliation. This was attributed to the streptomycin, which was then abandoned. His clinical condition worsened rapidly. The blood urea nitrogen rose to 140 mg. per cent, which was apparently an unusually toxic response to streptomycin. For this, intravenous procaine therapy was given, with prompt amelioration of the cutaneous-renal evidences of streptomycin sensitivity.

Intensive penicillin therapy was thereupon substituted on the forty-third hospital day. He received 10 million units daily for 20 days. The rash subsided and the blood urea nitrogen fell to 30 mg. per cent. Upon cessation of penicillin therapy, which totalled 200 million O.U., he continued to have a low grade fever which varied from 99° to 100.6° F. On two occasions during the succeeding three weeks, it reached 101° F. After that the temperature fell to a normal level, where it remained. After the twenty-fifth day the blood cultures were repeatedly negative.

Because of several episodes which suggested pulmonary infarction, he received a successful course of anticoagulation therapy with heparin/Pitkin Menstruum.[25] The

heart failure cleared up and he was discharged on the one hundred third hospital day.

He was subsequently seen one year after the onset of his illness and was found to be in surprisingly good health. He had gained weight, was fully ambulatory and had little or no discernible residue from his severe infection.

COMMENT

This case is that of a 55 year old white male with subacute enterococcus endocarditis deriving from the urinary tract. There was no antecedent cardiac history. The diagnosis was suspected early and vigorous treatment instituted from the outset. In spite of the severe clinical picture, the marked congestive heart failure and the serious drug sensitivity, he made an excellent recovery.

The early diagnosis and prompt inauguration of suitable therapy prevented the complications which compromised the results in cases 2, 3 and 5. Furthermore, the inaugural treatment program was adequate and remained so throughout. Despite the comparatively favorable streptomycin in vitro values, this antibiotic had to be abandoned in favor of penicillin, which proved to be nontoxic and curative. The eminently satisfactory penicillin blood levels may have been due to the transitory impairment of renal function induced by the streptomycin.

DISCUSSION

Subacute enterococcal endocarditis has been considered a relatively rare disease. Of 624 cases of subacute bacterial endocarditis treated at The Mt. Sinai Hospital over a period of 20 years, 26 were caused by enterococci, an incidence of 3.2 per cent.[22] This compares with our percentage incidence of 3.8 in a series of 157 patients who had subacute bacterial endocarditis with known infective organisms (table 1). Sirota, Gerber and Baehr[22] reported on four cases which received chemotherapy; in one case, cure was obtained by means of penicillin and heparin. The infecting organism happened, fortunately, to be uncommonly sensitive to penicillin. In another, a temporary remission was obtained by means of streptomycin alone. In two remaining cases, penicillin was combined with massive doses of sulfonamides; the result was complete failure. Cases of apparently spontaneous remission of enterococcus endocarditis have been recorded in the literature.[29] Since the introduction of antibiotics in the therapy of subacute enterococcus endocarditis, a total of but three cases of apparently clinical cure have been reported.[19, 20, 21]

The enterococcus, which commonly inhabits the gastrointestinal tract, is a highly resistant streptococcus with distinctive characteristics. Although mostly saprophytic, it is frequently responsible for genitourinary infections and those complicating perforate lesions of the gastrointestinal tract. It is often the infective agent in septic abortions and bacteremias which stem from the genitourinary or the gastrointestinal tract.

The important biologic characteristics, as described by Sherman,[20,21] which permit the identification of enterococci are the capacity of these bacteria to grow well at 10° C. and 45° C. in the presence of 6.5 per cent sodium chloride, 0.1 per cent methylene blue and a pH of 9.6, and to resist heating for 30 minutes at 60° C. Practically all of the streptococci which fulfill these biologic requirements will be found serologically to be members of the Lancefield group D.

The enterococci are capable of growth in ordinary laboratory mediums used for routine blood culture. They resemble pneumococci so closely that special studies are necessary to differentiate them. In our experience, the organisms always proved to be hardy in artificial mediums and grew out readily without recourse to special culture mediums or anaerobic technics. As a result, no difficulty was encountered at any time in obtaining positive blood cultures from patients with subacute enterococcus endocarditis. This is contrary to experience in subacute bacterial endocarditis due to other infecting organisms, where there is an anticipated failure to obtain positive blood cultures in 10 to 15 per cent of the patients. In the event of relapse of the infection after antibiotic therapy, the organisms reappear rapidly and can be recovered with ease. The newly isolated organisms should be reinvestigated as to penicillin and streptomycin sensitivity. It is a well known fact that organisms, when exposed to a sublethal concentration of an antiinfective drug, at times acquire resistance to the agent in question. This phenomenon has not occurred with the enterococcus group, although our experience is much too limited to postulate that it never develops.

It is evident from table 4 that five of the six enterococcus strains displayed resistance to penicillin which was 12.5 times the M.L.D. value for the most refractory of the 139 nonhemolytic streptococci processed in our series of 157 patients with subacute bacterial endocarditis (table 1). The range of penicillin test tube sensitivity of these 139 organisms was 0.008 to 2.0 O.U. per ml., as compared with the range of 12.5 to 25 O.U. for the enterococcal strains. Our clinical experience has shown that it is possible to treat infections successfully with penicillin even when the in vitro sensitivity value of the causative organism is 25 O.U. per ml. of test broth. All the enterococci, with the exception of case 6, showed resistance to streptomycin of an unusually high order, so much so that attaining effective levels in vivo would have entailed the use of toxic dosages of the drug. In point of fact, the use of streptomycin in diseases like subacute enterococcal endocarditis poses a very definite problem because of the anticipated toxic effects of the requisite long span, high level therapy. It is possible that this objection may be overcome by the newer, less toxic dihydrostreptomycin. In case 6, the only instance in the series where streptomycin was available in quantity and indicated from the test tube values, great difficulty was encountered in the use of this antibiotic. It ultimately had to be abandoned in favor of penicillin because persistence with streptomycin would probably

have been disastrous in view of the severe unremitting toxic effects ascribable to the drug.

It is evident from the in vitro sensitivity data and from actual observations with these refractory organisms that the treatment plan must envisage the use of at least 10 million O.U. of penicillin daily. For optimal curative purposes, penicillin blood assays at all times must at least parallel the in vitro M.L.D. value. This can be best accomplished by administering the penicillin in continuous venoclysis, together with augmenting agents such as Staticin.[32] It is quite possible that some of the four patients who succumbed might have been salvaged with the current treatment programs, even though they appeared profoundly deteriorated. Penicillin proved to be the drug of choice for routine use in patients with subacute enterococcus endocarditis, although the conjoint use of streptomycin for even a short span might conceivably have exerted some favorable influence in the two recovered patients.

Unlike other nonhemolytic streptococci, the enterococcus is unique in that it has a pronounced tendency to induce pyogenic and encapsulated lesions. The invasive property of the enterococcus is evidenced by the fact that it attacks normal heart valves (cases 1 and 6), differing from the customary form of subacute bacterial endocarditis, which is invariably engrafted on a primary cardiac lesion of acquired or congenital nature. Therefore, in order to authenticate a diagnosis of subacute enterococcus endocarditis, it is not necessary to obtain a history of some antecedent cardiac lesion. Suppuration of the myocardium and other viscera is a fairly common occurrence. Splenic rupture with fatal peritonitis due to septic infarctions has been reported in this disease. Focal myocardial lesions are common, and an enterococcus myocarditis is of almost uniform incidence.

The cardiac status, particularly the extent of the myocardial lesions, has much to do with dictating a successful outcome. If the lesions are too severe the patient will not survive to receive the benefits of the therapy. The degree of heart damage and consequent heart failure also determine the extent and efficacy with which the treatment program can be conducted. Obviously, the greater the heart failure the less readily can intensive, massive, optimal antibiotic therapy be given uninterruptedly for the requisite span of time. The degree of mutilation of heart valves and the measure of residual myocardial damage are important prognostic factors, not only during the actual treatment but also in the post-therapy period.

Renal, splenic and the more ominous cerebral embolizations were not encountered often in our series of enterococcus patients. In a comparable series of very ill patients suffering with subacute bacterial endocarditis due to *Streptococcus viridans,* embolization even of a lethal nature could be anticipated much more frequently. Perhaps the nature of the vegetations in enterococcus endocarditis may have something to do with this phenomenon, inasmuch as the ulcerative, undermined type of endocarditic lesions is observed rather than the customary exuberant, friable, thrombotic, cauliflower-like masses.

It cannot be overemphasized that this disease calls for heroic, intensive, massive therapy instituted promptly. Procrastination and inadequate dosage lead rapidly to irreversible valve damage and promote the development of severe complications, such as mycotic aneurysms of the sinuses of Valsalva, with extension of the infection into the pericardium and pyogenic lesions of the myocardium. These complications are invariably fatal, regardless of the subsequent treatment programs. It is possible to sterilize the blood stream and the surfaces of the infected valves without favorably affecting the clinical course. No amount of intensive therapy will suffice to sterilize the metastatic, encapsulated, purulent lesions which serve as seeding foci.

Of the six cases in our series, five had been treated elsewhere and were considered treatment failures at the time of admission to our institution. It is significant that case 6 recovered despite the extreme degree of morbidity, due probably to the fact that the diagnosis was made relatively early in the course of the illness and an adequate treatment program was instituted promptly. Our other proved success may be ascribed in part to the fact that he was treated with liberal dosages of penicillin which suppressed the infection. As a result, the development of lethal, infarctive, suppurative encapsulated lesions was prevented.

Not included in this series is a seventh patient, a 49 year old female with subacute enterococcus endocarditis who completed her therapy only three weeks ago. While it is premature to catalog this case as a cure, she fulfills all the criteria of a recovered case of enterococcus endocarditis as judged by her clinical appearance, negative blood cultures, improved hematologic picture and normal erythrocyte sedimentation rates. It is significant that this patient was originally diagnosed and the infecting agent identified within four weeks of onset of the illness, following which adequate treatment was promptly instituted. The presumably curative treatment program consisted of (1) 1 million units of penicillin every three hours intramuscularly, totalling 8 million units daily; (2) Staticin by mouth, 4 gm. every four hours for enhancing purposes, and (3) dihydrostreptomycin,* 0.5 gm. every six hours intramuscularly, all for a period of five weeks.

Miscellaneous factors may compromise an otherwise successful result or, at any rate, confuse the clinical picture. This occurred in case 4, where there was a drug sensitivity that simulated rheumatic fever. There was no diagnostic difficulty in this particular instance but merely some question as to whether the enterococcus infection still persisted, calling for additional therapy. Problems of a kindred nature were encountered in our series of subacute bacterial endocarditis where rheumatic disease actually coexisted or entered the clinical picture in the post-therapy period. As a result, we have been on guard for this complication. It is of more than academic interest to establish the presence of rheumatic fever, because continuation

* The dihydrostreptomycin for this patient was kindly supplied by E. R. Squibb & Sons, New York.

of antibiotic therapy under these circumstances will not only complicate the clinical picture but may in fact result disastrously as far as the rheumatic disease is concerned. Rheumatic patients are known to be unfavorably affected by massive doses of penicillin.[33, 34] Troublesome drug sensitivities may be observed in connection with streptomycin treatment. The unfavorable response to streptomycin in case 6 was unique; he developed not only severe allergic phenomena but also a surprising degree of urea retention. The urea retention receded promptly when streptomycin therapy was suspended and procaine was administered intravenously to counteract the allergic manifestations.

PROPOSED TREATMENT PROGRAM FOR SUBACUTE ENTEROCOCCUS ENDOCARDITIS

If at all possible, the infection must be terminated with the first span of treatment. The antibiotic of choice is penicillin given intravenously, the vehicle being Ringer's solution or, in cases of congestive heart failure, 5 per cent glucose in distilled water. The venoclysis should not exceed 1,000 ml. allocated over a 24 hour period; at times, this may be restricted to 750 ml. This small amount of fluid can be administered in 24 hours only because heparin is used in the treatment program.

The heparin is incorporated for four reasons: (1) By using modest doses of heparin (50 mg. daily), which is incorporated in the venoclysis, it is possible to give the treatment over an uninterrupted period of time without incurring any of the hazards of larger dosages of heparin. No serious complications due to heparin have been encountered in the last 150 cases since this dosage of heparin was adopted. (2) It exhibits regional antibiotic effects, permitting the use of small 25 gauge needles in veins around the wrist or forearm and thereby allowing mobility of the patient. (3) It prevents deposition of thrombotic masses on the valves and promotes repair of the endocarditic lesions. (4) It neutralizes the thrombosing influence of the large dosages of penicillin which are required in the treatment of this disease.

For reasons already stated, we feel that an initial dose of 10 million units a day is desirable until the infecting organism is processed through the laboratory and penicillin and streptomycin test tube values are available. In the absence of such data, the clinical behavior is reflective of the response to the therapy. The blood levels on this dosage plan should be determined and reviewed with the sensitivity data, following which the treatment program can be properly orchestrated. If it is noted that ineffective blood levels are obtained with penicillin in the usual dosage of 10 million units a day, additional penicillin can be given, and enhancing agents such as Staticin should be included. In previously untreated cases, obtained early, a span of treatment of not less than five weeks should be projected. If the patient has deteriorated, or has had previously subcurative treatment, an eight week span of treatment is recommended.

If congestive heart failure has already developed, dehydration measures should be instituted concurrently. These can take the form of mercurial diuretics as indicated, with rigid limitation of fluids. The venoclysis should be restricted to 750 ml. and the diluent changed to 5 per cent dextrose in distilled water. The diet should be of the salt-poor variety, preferably with daily total sodium chloride content of less than 1 gm. In the presence of myocardial embarrassment, digitalis should be prescribed in the manner and dosage indicated.

If an undue amount of dyspnea supervenes, or if there are signs of serious right or left side heart failure, the intravenous infusion should be interrupted temporarily and dehydration measures intensified. The penicillin can then be given intramuscularly with or without enhancing agents, depending upon the blood level objective. The venoclysis can be started again as soon as the myocardial embarrassment is ameliorated.

Supportive measures, such as transfusions, hematinics, multivitamin preparations, etc., should be incorporated in the treatment program as indicated.

If, despite adequate blood levels, the patient's condition, temperature chart, lack of improvement in well being and absence of response in the hematologic picture all suggest that the infection is not being satisfactorily controlled, streptomycin should then be added to the treatment program. Streptomycin is employed best for short span treatment and is not, as already stated, the ideal single antibiotic for the type of refractory disease represented by subacute enterococcus endocarditis. However, cures unobtainable by the use of penicillin or streptomycin alone may, at times, be accomplished by a combination of the two antibiotics. Perhaps dihydrostreptomycin or some of the newer antibiotics will permit long term intensive dosage without fears of (1) toxicity and (2) development of bacterial resistance.

Finally, in the presence of rheumatic heart disease or a congenital cardiac lesion, a tooth extraction or a surgical, obstetric or gynecologic procedure may well provoke an attack of subacute bacterial endocarditis. It is wise to protect these susceptible individuals with adequate amounts of penicillin prior to, during and following any such procedures. The patient with rheumatic disease who is having a rectal or genitourinary operation is exposed to the more resistant enterococcus and, therefore, the prophylactic dosage of penicillin should be commensurate. Under these circumstances, 8 million units a day, in divided dosage, is not excessive.

SUMMARY AND CONCLUSIONS

1. Of 157 patients with subacute bacterial endocarditis due to known organisms who received antibiotic therapy, six (3.8 per cent) were infected with the resistant enterococcus.

2. These six patients with subacute enterococcus endocarditis served to evolve a rational therapeutic program for this refractory disease.

3. The factors responsible for the four treatment failures were analyzed.

4. Two of the six patients recovered following prolonged, massive and, at times, combined antibiotic therapy.

5. A curative treatment program has been developed for routine use in patients with subacute bacterial endocarditis due to the enterococcus or other resistant infecting organisms.

6. A seventh patient with subacute enterococcus endocarditis has responded promptly, and apparently successfully, to this current, optimal treatment program.

BIBLIOGRAPHY

1. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M.: Combined penicillin and heparin therapy of subacute bacterial endocarditis—report of seven consecutive successfully treated patients, J. A. M. A. **124**: 144, 1944.

2. Loewe, L.: The combined use of penicillin and heparin in the treatment of subacute bacterial endocarditis, Canad. M. A. J. **52**: 1, 1945.

3. Loewe, L., Rosenblatt, P., and Greene, H. J.: Combined penicillin and heparin therapy of subacute bacterial endocarditis, Bull. New York Acad. Med. **22**: 270, 1946.

4. Loewe, L., and Eiber, H. B.: Subacute bacterial endocarditis of undetermined etiology, Am. Heart J. **34**: 349, 1947.

5. Dawson, M. H., and Hunter, T. H.: Treatment of subacute bacterial endocarditis with penicillin: results in twenty cases, J. A. M. A. **127**: 1945; Ann. Int. Med. **24**: 170, 1946.

6. Bloomfield, A. L., and Halpern, R. M.: Penicillin treatment of subacute bacterial endocarditis: some problems, J. A. M. A. **129**: 1135, 1945.

7. Goerner, J. R., Geiger, A. J., and Blake, F. G.: Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents, Ann. Int. Med. **23**: 491, 1945.

8. Flippin, H. F., Maycock, R. L., Murphy, F. D., and Wolferth, C. C.: Penicillin in treatment of subacute bacterial endocarditis: preliminary report on twenty cases treated over one year ago, J. A. M. A. **129**: 841, 1945.

9. Meads, M., Harris, H. W., and Finland, M.: Treatment of pneumococcal pneumonia with penicillin, New England J. Med. **232**: 463, 1945.

10. Paullin, J. E., and McLoughlin, C. J.: The treatment of subacute bacterial endocarditis with penicillin, Ann. Int. Med. **22**: 475, 1945.

11. Christie, R. V.: Penicillin in subacute bacterial endocarditis: report to Medical Research Council on 147 patients treated in 14 centers appointed by Penicillin Clinical Trials Committee, Brit. M. J. **1**: 381, 1946.

12. Favour, C. B., Janeway, C. A., Gibson, J. T., II, and Levine, S. A.: Progress in treatment of subacute bacterial endocarditis, New England J. Med. **234**: 71, 1946.

13. Glaser, R. J., Smith, R. O., Harford, C. G., and Wood, W. B., Jr.: Treatment of bacterial endocarditis with penicillin, J. Lab. and Clin. Med. **31**: 291, 1946.

14. Mokotoff, R., Brams, W., Katz, L. N., and Howell, K. M.: Treatment of bacterial endocarditis with penicillin: results of 17 consecutive, unselected cases, Am. J. M. Sc. **211**: 395, 1946.

15. Ward, G. E. S., Meanock, R. I., Selbie, F. R., and Simon, R. D.: Treatment of subacute bacterial endocarditis by penicillin: preliminary report on 18 cases, Brit. M. J. **1**: 383, 1946.

16. Meyer, O. O., and Thill, C. J.: Penicillin and Dicumarol in treatment of subacute bacterial endocarditis, J. Lab. and Clin. Med. **31**: 487, 1946.

17. Massell, B. F., and Jones, T. D.: Subacute bacterial endocarditis: report of 2 cases successfully treated with penicillin, New England J. Med. **235**: 605, 1946.

18. Herring, A. C., and Davis, W. M.: Penicillin treatment of subacute bacterial endo-carditis: report of eighteen consecutive cases, J. A. M. A. **138**: 726, 1948.
19. Baehr, G.: Penicillin treatment of subacute bacterial endocarditis due to enterococcus, Regional Meeting, Am. Coll. Phys., State of N. Y., N. Y. C., Oct. 1944.
20. Harris, R.: Subacute bacterial endocarditis: report of enterococcal infection treated with penicillin, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. **8**: 61 (Oct.) 1945.
21. MacNeal, W. J., Blevins, A., and Poindexter, C. A.: Clinical arrest in enterococcal endocarditis, Am. J. M. Sc. **211**: 40, 1946.
22. Sirota, J. H., Gerber, I. E., and Baehr, G.: Chemotherapy of subacute enterococcus endo-carditis, J. Mt. Sinai Hosp. **14**: 604, 1947.
23. Rosenblatt, P., Alture-Werber, E., Kashdan, F., and Loewe, L.: A method for the determination of penicillin levels in body fluids, J. Bact. **48**: 599, 1944.
24. Alture-Werber, E., and Loewe, L.: A method for routine determination of streptomycin levels in body fluids, Proc. Soc. Exper. Biol. and Med. **63**: 277, 1946.
25. Loewe, L.: Anticoagulation therapy with heparin/Pitkin Menstruum in thromboembolic disease, Am. J. Med. **3**: 447, 1947.
26. Werber, E. A., Shore, M. K., Menkes, E. C., and Loewe, L.: The clinical correlation of in vitro penicillin sensitivity tests, Bull. New York Acad. Med. **22**: 477, 1946.
27. Loewe, L., and Alture-Werber, E.: Streptomycin dosage schedules for clinical use, Bull. New York Acad. Med. **23**: 589, 1947.
28. Loewe, L., Rosenblatt, P., and Alture-Werber, E.: A refractory case of subacute bac-terial endocarditis due to *Veillonella gazogenes* clinically arrested by a combination of penicillin, sodium para-aminohippurate and heparin, Am. Heart J. **32**: 327, 1946.
29. Bito Del Pino, J. A., Osimoni, J. J., and Digbiro, J. C.: Acute endocarditis due to enterococcus, cured or in unmistakable remission, Arch. urug. de med., cir. y. especialid. **8**: 383, 1936.
30. Sherman, J. M., and Stark, P.: Streptococci which grow at high temperatures, J. Bact. **22**: 275, 1931.
31. Sherman, J. M., and Stark, P.: The differentiation of *Str. lactis* from *Streptococcus fecalis*, J. Dairy Sc. **17**: 525, 1935.
32. Loewe, L., Eiber, H. B., and Alture-Werber, A.: Enhancement of penicillin blood levels following oral administration of caronamide, Science **106**: 494, 1947.
33. Watson, R. F., Rothbard, S., and Swift, H. F.: Use of penicillin in rheumatic fever, J. A. M. A. **126**: 274, 1944.
34. Foster, F. P., McEachern, G. C., Miller, J. H., Ball, F. E., Higley, C. S., and Warren, H. A.: Treatment of acute rheumatic fever with penicillin, J. A. M. A. **126**: 281, 1944.

VARIATIONS IN URINARY DILUTION AND CONCENTRATION AMONG HEALTHY MALES UNDER SIMPLE STANDARD CONDITIONS [*]

By W. Edward Storey, M.D., *Columbus, Georgia*

The tests of urinary dilution and concentration, particularly the latter, are generally regarded as a simple and reliable means of detecting early impairment of renal function. They are based upon the fact that healthy kidneys can adapt, within wide limits, to varying demands for the elimination of water and solids. This adaptability may be observed in the specific gravity of the urine under controlled conditions.

Since the publication, in 1910 of Volhard's [1] technic for the performance of these tests, various modifications have appeared.[2, 3, 4, 5, 6, 7] While each of these has acquired varying acceptance, that of Fishberg [8] is probably the most widely used at the present time. This is due, in large measure, to its simplicity.

Fishberg has used his modification in several thousand healthy and diseased persons and, apparently, is satisfied with its usefulness. However, he has not assembled in any publication the results of his observations among healthy subjects.[9] Mosenthal [10] tried a similar modification and reported a study of 100 healthy medical students but, because about 10 per cent of his subjects failed to concentrate to 1.020, he was not convinced of its reliability. Therefore, he adhered to the more elaborate procedure already known by his name.[3] Although there are numerous reports upon tests of this type in various pathologic states, it appears that their application to persons of demonstrably good health has had comparatively little attention in the literature. Thus, as late as 1926 Pratt [4] could find reported only six healthy subjects to whom the Volhard procedure had been applied. To this collection, he added 26 subjects whose common diagnosis was psychoneurosis. The other reports which I have been able to find concerning normal variations have involved rather small numbers of subjects, and usually little, if anything, has been said of the pains taken to establish the absence of defects likely to influence results.

Whoever accumulates experience with any of the tests of urinary dilution or concentration is impressed, sooner or later, with the divergence sometimes seen between the results obtained and the bedside impression of the patient's condition.

The author wishes to emphasize the care with which the present subjects were selected to exclude any factor likely to impair maximal response to the

tests. The importance of such an effort for evaluation of results in various disease states is obvious. Moreover, it is not the author's intent to attempt to pass judgment upon the validity of the Fishberg type of test. Instead, the present account is offered merely to record one man's experience with it under carefully established normal conditions. It is hoped that others may be prompted to record their experiences and that thus some broad basis for judgment may eventually be accessible to those interested in renal function.

MATERIAL AND METHODS

The subjects of this study were 96 white males whose ages ranged from 18 to 50 years. They were under observation because of simple overweight or underweight, minor orthopedic defects or psychoneurosis. Some awaited such elective operations as herniorrhaphy or dental prosthesis. Their selection began with a complete clinical history which, in addition to the usual survey of systems, included questions designed to eliminate all whose past history indicated any of the diseases prone to significant involvement of the renal, cardiovascular or endocrine systems. The family history gave due consideration to such items as polycystic renal disease, diabetes mellitus, sudden deaths and premature arteriosclerosis. No subject had ever been suspected of abnormal blood pressure or heart disease, however efficient the circulation might be currently. None had ever taken digitalis or diuretics. Nothing indicated previous disease of the bladder or prostate and none had had syphilis, exposure to mercury or to other nephrotoxic chemicals. In the older subjects, vascular texture was well within allowable limits for age, and there had been nothing to suggest the masculine climacteric or other endocrine imbalance.

Physical examination was complete, with special attention to eyegrounds, heart, blood pressure and rectal examination. None had palpable kidneys, any type of edema or any degree of premature vascular deterioration. Each had at least one preliminary normal urinalysis upon the first morning specimen, and all had a normal complete blood count, stool examination, serologic test for syphilis, fasting blood non-protein-nitrogen and blood sugar. Every subject was given a Van Slyke urea clearance test [11] and an intravenous phenolsulfonphthalein test which was computed for 15, 60 and 120 minutes, according to the method of Chapman and Halsted.[12]

No subject was febrile. There was complete abstinence from alcohol and there were no drug effects during the week of the tests. Each had subsisted upon a general, well balanced diet during the week preceding the tests, and had consumed fluids in accordance with the dictates of thirst. No attempt was made to administer any specified amount of water, but no subject showed evidence of excessive or deficient hydration. The tests were done on separate days, usually three or four days apart, and with the concentration test followed by that of dilution. All instructions to patients, measurements and computations were made by the author and not left to

TABLE I

Summary of Data on Dilution and Concentration Tests in 96 Subjects *

Total Cases	Per Cent of Total	Maximum Concentration	Maximum Dilution	Water Output Per Cent of Total
1	0.96	1.038	1.001	175.8
2	2.0	1.035	1.001	140
3		1.034	1.001	139
4		1.034	1.001	135
5	5.2	1.034	1.001	128.1
6		1.032	1.001	126
7		1.032	1.001	120.5
8		1.032	1.001	114
9	9.3	1.032	1.001	112.4
10		1.031	1.001	106
11	11.4	1.031	1.001	103.8
12		1.030	1.001	97.1
13		1.030	1.001	96.6
14		1.030	1.001	96.4
15		1.030	1.001	96
16		1.030	1.001	91.8
17		1.030	1.001	91.2
18		1.030	1.001	91.2
19	19.7	1.030	1.001	90.4
20		1.029	1.001	89.1
21		1.029	1.001	87.7
22		1.029	1.001	86.6
23		1.029	1.001	85
24	25.0	1.029	1.001	83.1
25		1.028	1.001	82
26		1.028	1.001	81.5
27		1.028	1.001	81.5
28		1.028	1.001	80.1
29		1.028	1.001	80
30		1.028	1.001	79.9
31		1.028	1.001	78.3
32		1.028	1.001	77.3
33		1.028	1.001	76.7
34		1.028	1.001	75.3
35	36.4	1.028	1.001	75
36		1.028	1.002	74.6
37	38.5	1.028	1.002	74.3
38		1.027	1.002	74.2
39		1.027	1.002	74.1
40		1.027	1.002	73.6
41	42.6	1.027	1.002	73.5
42		1.026	1.002	71.2
43		1.026	1.002	71
44		1.026	1.002	70.8
45		1.026	1.002	68.6
46		1.026	1.002	68.6
47	48.9	1.026	1.002	68.3
48		1.025	1.002	66.6
49		1.025	1.002	65
50		1.025	1.002	64.8
51		1.025	1.002	64.3
52		1.025	1.002	64
53		1.025	1.002	63.7
54		1.025	1.002	63.3

* Each column is independent of the others and is tabulated in order of degree of response of the entire group. Percentages are given only as necessary in reference to variations in response.

TABLE I—*Continued*

Total Cases	Per Cent of Total	Maximum Concentration	Maximum Dilution	Water Output Per Cent of Total
55	57.2	1.025	1.002	63.1
56	58.3	1.024	1.002	62.5
57		1.024	1.003	61.2
58		1.024	1.003	60.8
59		1.024	1.003	59.2
60		1.024	1.003	58.1
61		1.024	1.003	58
62		1.024	1.003	57
63	65.6	1.024	1.003	56.3
64		1.023	1.003	54.9
65		1.023	1.003	54.1
66		1.023	1.003	54
67	69.7	1.023	1.003	53.4
68		1.022	1.003	53.3
69		1.022	1.003	53.3
70		1.022	1.003	53
71		1.022	1.003	51.6
72		1.022	1.003	51.3
73	76.0	1.022	1.003	51
74		1.021	1.004	50
75		1.021	1.004	49.5
76		1.021	1.004	49.1
77	80.2	1.021	1.004	47.5
78		1.020	1.004	44.5
79		1.020	1.004	44
80		1.020	1.004	42.5
81		1.020	1.004	42
82		1.020	1.004	39.6
83	86.4	1.020	1.004	39.5
84		1.020	1.005	37.5
85		1.020	1.005	36.6
86		1.020	1.005	35.9
87		1.020	1.005	34.5
88	91.6	1.020	1.005	32.5
89	92.6	1.019	1.005	32
90		1.018	1.006	31.6
91		1.018	1.006	31.6
92	95.8	1.018	1.006	30.4
93	96.8	1.018	1.007	22.9
94	97.8	1.016	1.008	20.4
95	98.9	1.015	1.013	16.9
96	100.00	1.015	1.017	15.6

others. Appropriate correction was made for temperature in the determination of specific gravity.

Dilution Test: At 8:00 a.m. the fasting patient emptied his bladder and drank 1,200 c.c. of cool water within five minutes. Thereafter he remained quietly sitting or lying, without further liquid or food, until the test was completed. The bladder was completely emptied into separate containers hourly until three specimens were collected and the test was ended. (Fishberg collects a fourth hourly specimen.)

Concentration Test: On the day before the test, after the noon meal at which usually not more than 200 c.c. of fluid were taken, subject took no food or liquid except a light supper at 6 p.m. This consisted of meat, rolls and potatoes, and was eaten without fluid of any kind. Thereafter, nothing

was taken by mouth until completion of the test on the following morning. Subject remained quietly on the ward and at bedtime the bladder was emptied and specimen discarded. At 6:00 a.m. the bladder was emptied into the first container. Subject remained quiet, though not necessarily in bed, and without food or liquid until further specimens were collected at 8:00 and 10:00 a.m., thus ending the test. (Fishberg collects the three specimens one hour apart, as at 8, 9 and 10 o'clock.)

RESULTS

Concentration Test: Table 1 presents the results with both tests in the order of degree of response. The maximal concentration was 1.038 and the minimal was 1.015, with an average of 1.025 for the group. Seventy-three subjects (76 per cent) concentrated to Fishberg's standard of 1.022 or

TABLE II

Analysis of Individual Responses to Concentration and Dilution Tests

Group I Concentration Satisfactory Dilution Satisfactory	Fishberg's Standards (C: 1.022 plus; D: 1.002 minus)	.35(36.4%)	
	Proposed Standards (C: 1.020 plus; D: 1.005 minus)		81(84.3%)
Group II Concentration Satisfactory Dilution Unsatisfactory	Fishberg's Standards (C: 1.022 plus; D: 1.003 plus)	38(39.5%)	
	Proposed Standards (C: 1.020 plus; D: 1.006 plus)		6(6.2%)
Group III Concentration Unsatisfactory Dilution Satisfactory	Fishberg's Standards (C: 1.021 minus; D: 1.002 minus)	21(21.8%)	
	Proposed Standards (C: 1.019 minus; D: 1.005 minus)		8(8.3%)
Group IV Concentration Unsatisfactory Dilution Unsatisfactory	Fishberg's Standards (C: 1.021 minus; D: 1.003 plus)	2(2%)	
	Proposed Standards (C: 1.019 minus; D: 1.006 plus)		1(0.96%)
	Totals	96	96

higher with a single test. Of the remaining 23 subjects (24 per cent) who failed to attain the standard under test conditions, nine had already shown a concentration of 1.022 or higher in the first morning specimen, done as a preliminary to selection for study (table 4). Further tests were not done on these subjects. Among the final 14 subjects who did not attain 1.022 at the first test, six were given one or more additional concentration tests, but only two attained 1.022, one of them not until the fourth attempt. Of two others, who did attain the standard initially but were nevertheless retested, one improved by 11 points at the second test. These data are shown in table 3.

Dilution Test: The maximal dilution was, of course, 1.001 and the minimal was 1.017, with an average of 1.002 for the 96 subjects. With a single test, 56 subjects (58.3 per cent) diluted to Fishberg's standard of 1.002 or lower, as shown in table 1. Among the 40 subjects who failed to attain the standard, with a single test, seven were given one or more additional tests, with an increase to 62 (64.5 per cent) who attained 1.002. Of four others, who did attain the standard initially but were nevertheless retested, two did less well by a point at the second test. These data are shown in table 3.

TABLE III

Summary of Results in Retested Subjects

Subject	Concentration Test					Dilution Test				
	First	Second	Third	Fourth	+	First	Second	Third	Fourth	- +
C. A. L.	1.018	1.018			0					
L. E. C.	1.018	1.019			1					
R. M. S.	1.016	1.019			3	1.001 (57%)*	1.001 (55%)			0
H. E. D.	1.014	1.021			7	1.004 (36.6%)	1.002 (111%)			- 2
S. B. M.	1.015	1.015	1.020	1.023	8	1.003 (51.6%)	1.001 (67%)			- 2
J. R. M.	1.020	1.023	1.023		3					
R. G. R.	1.025	1.027			2	1.004 (139.4%)	1.003 (79.7%)			- 1
M. N. A.	1.022	1.033			11					
H. M. R.						1.001 (86.6%)	1.002 (92.8%)			+ 1
N. P. J.						1.006 (51.2%)	1.001 (30.4%)	1.001 (21.4%)	1.001 (41.6%)	- 5
R. N. B.						1.002 (31.6%)	1.001 (62%)			- 1
H. N. G.						1.001 (36.6%)	1.002 (80.2%)			+ 1
A. G. B.						1.007 (32.5%)	1.002 (31.8%)			- 5
M. N. Y.						1.017 (22.9%)	1.012 (19.1%)	1.004 (35.2%)	1.001 (27.5%)	-16
J. A. M.						1.013 (20.4%)	1.003 (72.3%)	1.001 (30%)		-12

+ — Points of variation.
* Per cent water excreted.

Water Output: As shown in table 1, 11 subjects (11.4 per cent) excreted all the water during a three hour collecting period. (Fishberg collects during four hours.) If 75 per cent of the ingested water may be regarded as "the larger part" (Fishberg), then it is seen that 35 subjects (36.4 per cent) excreted that much in three hours. For the same period of time, 74 subjects (77 per cent) excreted half the amount taken.

Table 2 shows how many individuals conformed to Fishberg's standards with both tests, with either, or with neither of them. It also shows the same analysis based upon a slightly lower set of standards, which will be referred to later. Thus, it is seen that 35 subjects (36.4 per cent) met Fishberg's

TABLE IV

Subjects Who Concentrated to Higher Degree in First Morning Specimen
Than During Testing Procedure

No.	Subject	Sp. Grav. of 1st a.m. Spec.	Max. Sp. Grav. on First Conc. Test	Points Difference
1	H. R. S.	1.028	1.019	9 *
2	J. F. L.	1.027	1.018	9 *
3	E. B. K.	1.027	1.021	6 *
4	T. A. M.	1.026	1.020	6 *
5	C. F. H.	1.026	1.015	11 *
6	L. N. P.	1.024	1.020	4 *
7	R. N. T.	1.023	1.018	5 *
8	D. N. B.	1.023	1.020	3 *
9	H. N. G.	1.022	1.020	2 *
10	D. S. H.	1.033	1.029	4
11	N. G. W.	1.033	1.030	3
12	G. I. W.	1.032	1.024	8
13	C. W. M.	1.031	1.030	1
14	A. G. B.	1.030	1.029	1
15	S. N. T.	1.030	1.027	3
16	J. C. T.	1.029	1.028	1
17	J. A. G.	1.029	1.028	1
18	J. N. U.	1.025	1.022	3
19	R. N. T.	1.025	1.023	2
20	P. T. B.	1.025	1.024	1
21	R. S. S.	1.025	1.022	3
22	W. J. G.	1.024	1.022	2
23	J. T. S.	1.024	1.023	1
24	R. M. S.	1.018	1.016	2

* Referred to in Discussion.

standards for both tests.   Of these, 13 (37 per cent), or about a third, excreted as much as three-fourths of the ingested water during the three hour collection period.

COMMENT

The only liberties taken with Fishberg's directions for these tests were: (1) the adoption of a three-hour instead of a four-hour collection period for the dilution test; (2) failure to require subjects to remain in bed between collections of the first and second specimens in the concentration test, and (3) collection of concentrated specimens at intervals of two hours instead of hourly. These were adaptations suited to local circumstances, and it is doubtful whether they influenced results to a significant degree. In view of the pains taken to exclude all but healthy subjects and to enlist the enthusiastic coöperation of those selected, it is believed that these results are as nearly free of technical error as one might expect to achieve in a project involving coöperation among various humans.

At the beginning of this study it was not anticipated that 24 per cent of subjects would fail to concentrate to 1.022, that 42 per cent would fail to dilute to 1.002, and that only 36 per cent would eliminate three-fourths of the ingested water in three hours. It was supposed that the results with such a carefully chosen group would be greatly better. Unfortunately, the

number of subjects retested was not large. Although there is evidence that retesting will usually improve the results, sometimes it fails to do so and sometimes it does so only after repeated attempts.

Since it is believed that pathologic factors were excluded from these results, it is assumed that the considerable variability of response, as a group and in certain individuals, was due to physiologic factors not adequately controlled by the conditions specified for these tests. Comment upon the nature of these factors will not be attempted, except to say that the work of Mosenthal [3] and others seems to indicate that the chief influence is the quality of the diet preceding and during the tests. Undoubtedly other physiologic considerations enter, but their evaluation will be left to whoever has evidence concerning them, because the purpose of this report is to present the factual data obtained. Table 4 supports the impression that important variables are uncontrolled by the conditions specified for this type of concentration test. In 24 subjects, a simple first morning specimen, without fluid restriction, was more concentrated than any of the three specimens collected from the same subjects under the conditions of the test. These differences ranged up to 11 points.

Moreover, table 3 shows the considerable variability which may be seen in successive tests of certain individuals within a few days. For the concentration test, differences again ranged up to 11 points and for the dilution test up to 16 points.

Finally, these variable factors are further suggested by the amount of water excreted in the dilution test. Even when Fishberg's standard is interpreted broadly, this result was the most inconstant and unreliable of all. If the extremes are selected (table 1), it is seen that seven subjects excreted amounts of water ranging from 120 to 175 per cent of that ingested, while 10 others eliminated less than 35 per cent. All were tested strictly according to the stated outline. Similarly, there were certain individuals who, upon retesting, showed comparable variability (table 3). For example, H. E. D. excreted 36.6 per cent of the ingested water at first try and then a week later 111 per cent; H. N. G. also excreted 36.6 per cent at first and then later 80.2 per cent; J. A. M. first excreted 20.4 per cent, then 72.3 per cent, and finally 30 per cent, while successive tests reduced the specific gravity from 1.013 to 1.001. Others showed a more even elimination of water, while dilution improved with each repetition, as shown in table 3.

Although these findings suggest that this type of test should be interpreted with due care and repeated where doubtful, there is no reason to assume that it should be discarded. On the contrary, if certain modifications of the standards could be found acceptable, it might continue to deserve, with even more justification, the favor of most clinicians. Examination of tables 1 and 2 will show that if the standards were slightly modified, the proportions of subjects who conform at the first testing would be substantially increased and the tests thereby made more dependable for simple clinical estimates. Thus, if 1.020 (instead of 1.022) were adopted as the minimal

normal concentration, it is seen that 91.6 per cent of present subjects would conform. If, therefore, one out of 10 patients showed a doubtful result and required retesting, it would not unduly burden office or clinic facilities. Interestingly, the 9 per cent of present subjects accords with the 10 per cent of Mosenthal's [10] subjects who failed to concentrate to 1.020 with a comparably simple test. Similarly, if 1.005 (instead of 1.002) were permitted to be the minimal normal dilution, 92.6 per cent of present subjects would conform. Reference to table 2 shows, then, that these adjusted standards would allow 84.3 per cent of this group to meet the requirements of both tests, at least insofar as concentration and dilution are concerned, if not three hour excretion of water. Whether such adjustment of Fishberg's standards would be feasible would be best determined by further study.

SUMMARY AND CONCLUSIONS

1. A group of 96 males, whose ages ranged from 18 to 50 years, were carefully selected for absence of any factor likely to impair maximal renal function and were given tests of urinary concentration and dilution by a technic almost identical with that outlined by Fishberg. Results are presented.

2. With a single test, 76 per cent of subjects concentrated to 1.022 or higher and 58.3 per cent diluted to 1.002 or lower, in accordance with the standards set by Fishberg. Both of these standards were met by 36.4 per cent of subjects.

3. There is evidence that retesting will usually improve the result with each test, but not invariably and sometimes only after several attempts. Of six subjects who were given further concentration tests because they failed to attain the standard initially, only two succeeded and one of them not until the fourth attempt. Of seven subjects who were given further dilution tests for the same reason, six attained the standard, one only upon the third attempt and another not until the fourth attempt.

4. The amount of water excreted during the dilution test was the most inconstant and unreliable result in the present study. Only 36.4 per cent of subjects eliminated as much as three-fourths of the ingested water during the three-hour collection period. Extremes were 175.8 per cent and 15.6 per cent of the amount ingested. In certain individuals, successive tests varied from each other up to 300 per cent.

5. As a group and in certain individuals, there was wide variability of response to each test. This variability is assumed to result from physiologic factors not adequately controlled by the conditions of the tests. Discussion of these factors is not attempted, beyond pointing out that the work of others suggests that diet may be the principal consideration.

6. If Fishberg's standards for minimal normal concentration and dilution were modified to 1.020 and 1.005, respectively, the percentages of conforming normal subjects at the first testing would be substantially increased;

thus, 91.6 per cent would concentrate and 92.6 per cent would dilute "normally," and 84.3 per cent would meet the requirements of both tests. Whether such a modification would be feasible is not known to the author.

The author desires to thank Dr. Arthur M. Fishberg for encouragement and helpful criticism.

BIBLIOGRAPHY

1. Volhard, F.: Ueber die funktionelle Unterscheidung der Schrumpfnieren, Verhandl. d. deutsch. Kong. f. inn. Med. **27**: 735, 1910.
2. Hedinger, M., and Schlayer, C. R.: Ueber die Prüfung der Nierentätigkeit durch Probemahlzeit, Deutsch. Arch. f. klin. Med. **114**: 120, 1914.
3. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt, nitrogen and the specific gravity of urine, Arch. Int. Med. **16**: 733, 1915.
4. Pratt, J. H.: The dilution and concentration tests of renal function, Boston M. and S. J. **195**: 203, 1926.
5. Buck, R. W., and Proger, S. H.: The dilution and concentration test of renal function. Comparison of results with other tests in one hundred cases, New England J. Med. **203**: 1283, 1930.
6. Lashmet, F. H., and Newbergh, L. H.: Improved concentration test of renal function; simple method for measuring proteinuria, J. A. M. A. **100**: 1328, 1933.
7. Sodeman, W. A., and Englehardt, H. T.: Renal concentration test employing use of pituitary extracts. Response of normal subjects, Proc. Soc. Exper. Biol. and Med. **46**: 688, 1941.
8. Fishberg, A. M.: Hypertension and nephritis, ed. 4, 1944, Lea and Febiger, Philadelphia, p. 77.
9. Fishberg, A. M.: Personal communication.
10. Mosenthal, H. O.: Renal function as measured by the elimination of fluids, salt and nitrogen and the specific gravity of the urine. The application of the method to ambulant patients, M. Clin. North America **4**: 14, 209, 1921.
11. Moller, E., McIntosh, J. F., and Van Slyke, D. D.: Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults, J. Clin. Investigation **6**: 427, 1928.
12. Chapman, E. M., and Halsted, J. A.: Fractional phenolsulphonephthalein test in Bright's disease, Am. J. M. Sc. **186**: 223–232, 1933.

ELECTROCARDIOGRAPHIC FINDINGS IN CARDIAC ANEURYSM [*]

By Robert A. Steven, M.D., *San Francisco, California*

Introduction

The literature relating to the electrocardiographic findings in ventricular aneurysm is not very extensive, and almost all of it has appeared in the past 12 years. The relatively recent popularization of chest leads, plus the small number of cases seen by any one person, probably accounts for these facts.

In a recent study of 22 autopsied cases of ventricular aneurysm at the San Francisco Hospital, I became interested in the electrocardiographic changes as an aid in the diagnosis of this condition. These findings, plus those of certain other authors, form the basis of this report.

I have analyzed nine cases of true aneurysm and one of potential aneurysm. The other 13 cases of aneurysm either had bundle-branch blocks, or had no electrocardiograms taken at sufficient intervals after infarction, or no electrocardiograms at all, or the aneurysms were in the posterior wall.

Review of the Literature

In 1939, Eliaser and Konigsberg [1] described two patterns of limb lead changes in cardiac aneurysm based on five cases of their own and a larger number from the literature. These were described as an S_1 pattern and an $S_{2\,3}$ pattern. They found in the total collected group that 27.3 per cent showed the S_1 type and 36.4 per cent the $S_{2\,3}$ pattern, and felt that with either of these patterns one would have presumptive evidence of aneurysm. Nordenfelt,[2] in the same year, described very similar changes and, in addition, certain chest lead changes to be discussed later. Crawford [3] found the patterns described above in none of his 13 cases. In the 22 cases presented here, electrocardiograms were not available in six. Three cases showed right bundle-branch block and could not, therefore, be evaluated as to the two patterns mentioned. One case showed a large S_1 with a large R_3, but this was in a 26 year old girl, and such right axis is not too unusual at this age. Five cases showed a prominent S_2 and S_3, together with a good-sized R_1—in other words, a high degree of left axis deviation. Four of these cases had marked left ventricular hypertrophy. Only one had a normal-sized heart. The other seven cases showed neither pattern.

More encouraging are the electrocardiographic findings in the semi-direct chest leads taken over the aneurysmal changes. In Nordenfelt's [2]

eight cases, a single precordial lead was taken in four. Each of these four cases showed QS complexes, and the S–T segments were "elevated and passed directly into positive T waves." In his case 8, inspection shows deep QS complexes, absent R waves, slightly elevated S–T segments which are concave upward, and upright T waves. In case 7, S–T is slightly, if at all, elevated, and nearly horizontal, with neither convexity nor concavity, and T is nearly flat. He states: "in all probability there are no electrocardiographic changes so typical of aneurysm that they allow of a direct diagnosis." He suggests, however, "that if these findings remain unchanged for a long period following acute infarcts, there is reason to suspect chronic aneurysm or extensive fibrosis of the anterior wall of the left ventricle."

Crawford,[3] in 1943, in a presentation of 13 cases of aneurysm and a summary of the literature, stated in regard to diagnosis that "the electrocardiogram was of help only in establishing a previous coronary occlusion."

Wilson[4] stated in 1944, in part: ". . . Very pronounced R S–T displacement of the kind commonly seen in very recent anterior infarction was still present on November 7, 1941, when the first electrocardiogram was taken, and remained essentially unchanged on April 20, 1942 . . . complete healing of the infarcted muscle must have taken place long before the last curves were made. Ordinarily, pronounced R S–T displacement of the kind in question persists for a few hours, or, at most, for a few days. Why it persists in rare instances for weeks or months is still a mystery. In three cases of this sort, one of which was observed by Langendorf, a ventricular aneurysm was present, but it is possible that the association was due to chance. There is no known reason why ventricular aneurysm should displace the R S–T junction . . . in this way."

Thaon[5] reported five cases in 1947. Q S complexes and persistent S–T elevation in Lead IV F were present in two cases. All five cases showed left axis deviation and inverted T waves in Leads I and IV F.

Myers,[6] in his most excellent correlation of the electrocardiographic with the pathologic findings in 64 cases of anterior infarction, encountered four cases of aneurysm of the anterior wall. He states: ". . . an elevated, domelike, monophasic, upright R S–T segment and T wave or cove inversion of the T wave, identical with that found during recent infarction, may persist indefinitely as a fixed residue. This is especially prone to occur when there is extensive destruction and fibrous replacement of the wall, sufficient to lead to a ventricular aneurysm, as illustrated by the four patients. . . ." Inspection of these records shows QS complexes in four, elevated S–T in four, upward concavity of S–T in three, upward convexity in one, upright T waves in three, and diphasic (+ —) T waves in one. He feels that this pattern is derived from remote potentials, chiefly the intact posterior wall, picked up from the left cavity through the anterior window. One case with a vertical electrical position bears this out, as the pattern in aVF is almost the exact reciprocal of that in the precordial lead overlying the aneurysm.

Rosenberg,[1] in a study of four cases with roentgen-ray and kymographic signs of aneurysm, and four others with necropsy evidence of aneurysm, concluded that Q waves and persistent S–T elevation in chest leads were the essential electrocardiographic findings, but pointed out that three additional cases with autopsy proof of aneurysm failed to show these changes in a single (IV F) chest lead.   Six of their eight cases had a single (IV F) chest lead.   He feels that the ventricular complexes may be either QR or QS.

THEORETICAL CONSIDERATIONS

Transmural infarction of a fair-sized section of myocardium, plus complete destruction of all muscle elements therein, followed by fibrous replacement, would seem to be a sine qua non for the development of cardiac aneurysm of the type due to infarction.   Since the mere presence of bulging should contribute nothing to cardiac potentials, the electrocardiographic changes found over an area of complete fibrous replacement should be the same as those over an actual aneurysm.   In some cases, however, it is probable that aneurysm occurs before there has been time for much fibrous replacement.   It seems likely that most fair-sized areas of complete fibrous replacement will eventually bulge if the patient lives long enough, particularly if there is hypertension or other cause of cardiac strain.   For this reason, I have referred to such cases as "potential" aneurysms in this report.

An electrode over such "dead" areas should not record any R wave, but only a QS complex.   The presence of an R wave usually would arouse suspicion that the area contained some good muscle elements, or that the electrode was outside the dead area.   Myers'[6] explanation for the S–T–T changes usually seen seems adequate.

CASE REPORTS

Case 3. In this heart there was a distinct bulge of the anterior wall 8 cm. in diameter, beginning 3 cm. below the base. Over most of this section there was no myocardium. This bulge displaced the apex of the right ventricle toward the right. This infarct was old and extended into the anterior portion of the septum and the posterior tip of the apex. The apex in the region of the bulge extended 3.5 cm. beyond the tip of the right ventricle. The wall over the apical portion of this bulge was 2 to 3 mm. in thickness, and was composed of scar tissue. There was no involvement of the posterior wall, except for the tip of the apex. There was recanalization of the left anterior descending artery.

Three electrocardiograms (figure 1) had been taken at the time of the acute infarction five years before. On April 1, 1941, Lead IV F showed no Q, an R of 8 mm. and an S of 5 mm.; S–T was elevated 3.5 mm., and passed directly into an upright T. On April 18, Lead IV F showed a Q of 1.5 mm., an R of 7 mm., and an S of 10 mm.; S–T was elevated 3 mm., and distinctly coved, and T was deeply inverted. Coving of S–T without elevation had appeared in the limb leads; there were tiny Q waves in Leads II and III, and T was inverted in Leads I and II. On May 28, 60 days after the clinical onset of infarction, S–T elevation of 2 to 3 mm., with coving and deep inversion of T, persisted in Lead IV F. In addition, there were now tiny Q waves

in Leads I and II, marked coving of S–T$_1$, deep inversion of T$_1$, and diphasic (+ −) T$_2$.

The striking feature of the chest leads (IV F) in these tracings was the persistence of S–T elevation for 60 days, the time of the last tracing, after infarction. The R waves must have been due to potentials picked up lateral to the fibrosed area.
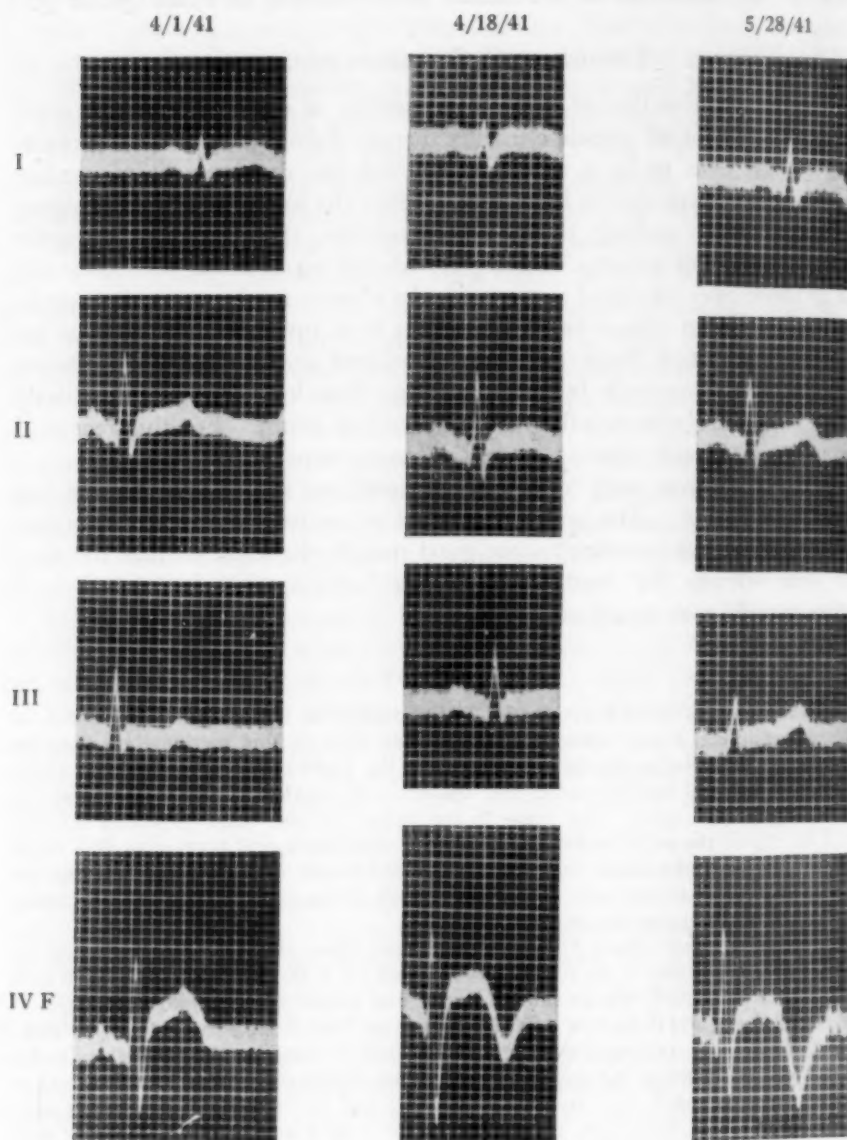

FIG. 1. *Case 3.*

Case 7. The apical half of the anterior left ventricular wall was 1 mm. in thickness, sharply demarcated from the hypertrophied muscle above it, replaced by fibrous connective tissue, and ballooned out to form an aneurysm. Both branches of the anterior descending artery were completely occluded by plaques. The posterior wall was not involved. Clinical onset was on July 10.
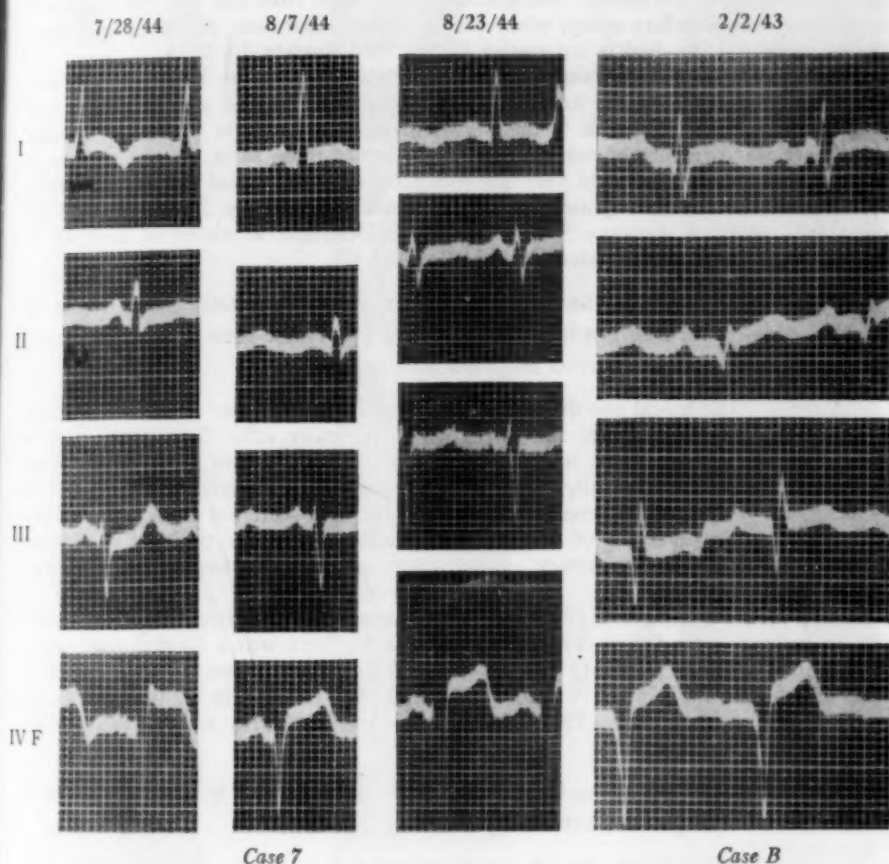
Fig. 2. Note the persistent S–T elevation in Lead IV F in both cases, and that these changes in case B (potential aneurysm) are practically identical with those in case 7 (actual aneurysm) on August 7, 1944.

Electrocardiograms (figure 2) were obtained on July 28, August 7, and August 23. Death occurred on September 11. On July 28, S–T was elevated 0.5 mm. in Lead I, depressed 1 mm. in Lead III, and elevated about 3.5 mm. in Lead IV F. S–T was coved in Lead I, and T₁ was inverted. S–T was concave upward in Lead IV F, and T was diphasic (+ −). On August 7, the S–T deviations were slightly less in extent in all leads; the S–T in Lead IV F was still concave, but the T in Lead IV F was now upright. On August 23, S–T was isoelectric in the limb leads, but was still elevated about 3.5 mm. in Lead IV F, and still concave. The T in Lead IV F was again diphasic (+ −). The complexes in Lead IV F were QS in all three electrocardiograms.

Thus, we see that elevation of S–T in the precordial lead was still present 43 days after the clinical onset of infarction.

Case B. This 49 year old female had had severe chest pain, dyspnea and orthopnea for the first time 10 months before entering the hospital on January 28, 1943, necessitating drugs for relief. She gradually recovered from this and was fairly well until three weeks before entry, when she developed shortness of breath and blood-tinged sputum. She died in congestive failure on February 12, 1943.

Autopsy showed an unusual degree of fibrosis of the lower half of the anterior left ventricular wall and the lower half of the septum. In this portion the left wall was 5 mm. in thickness, while in the basal half it was 20 mm. in thickness. In addition, there was evidence of more recent infarction of these same areas, plus some of the apical portion of the right ventricle extending into the apical portion posteriorly.

The one electrocardiogram (figure 2), taken on February 2, 1943, showed QS complexes, elevated, concave S–T segments, and upright T waves in Lead IV F. Abnormal Q waves were present in Leads II and III.

The recent infarct was probably three weeks old and the old one 10 months old. The changes in Lead IV F are like those seen in true aneurysm. The patient had not received digitalis at any time.

Case 8. The apical one-third of the anterior left ventricular wall had a purplish, cyanotic color, and the apical two-thirds was abnormally soft. Toward the apex of this area was a bulge 3 cm. in diameter. The wall was 3 mm. in thickness in the bulging area. Microscopically, this infarct appeared to be recent. There was no evidence of old infarction, except possibly for the old, scattered focal scars. There was no gross involvement of the posterior wall. There was thrombotic occlusion of the anterior descending artery. Some areas of patchy replacement fibrosis were present in the septum.

One electrocardiogram (figure 3) was taken six days after the clinical onset. The complexes were QS in V₁ through V₄. In V₅ there was a Q of 8 mm. and an R of 1 mm., while in V₆ the Q was 3.5 mm. and the R was 4 mm. The S–T take-off was 3 to 6 mm. high in the V leads. The S–T was concave in V₁ through V₃, and convex in V₄ through V₆. The T waves were upright in V₁ and V₂, and diphasic (+ −) in V₃ through V₆.

While six days may be too short a time, usually the S–T changes due to a current of injury will have disappeared in this time.

Case 21. This heart showed a distinct bulge 5 to 8 cm. in diameter near the apex, and the adjacent portion of the interventricular septum was involved, with bulging into the right ventricle. There was endocardial opacity over the major portion of the anterior and lateral walls of the left ventricle, and the anterior and inferior two-thirds of the septum. The anterior wall was thinned to as little as 3 mm. and was largely replaced by fibrous tissue.

Several tracings showed right bundle-branch block. In one record (figure 3) taken about one month before death and about five weeks after infarction, this block was absent. The complexes were QS in V₁ through V₃, R in V₄ and V₅, and RS in V₆. S–T was elevated about 2 mm. in V₁ through V₃, and passed directly into upright T waves. S–T was about isoelectric in V₄ through V₆.

Persistent S–T elevation and QS type of complex are again demonstrated in the first three chest positions. The aneurysm was predominantly antero-septal.

6 days after infarction   5 weeks after infarction

Case 8   Case 21

FIG. 3.
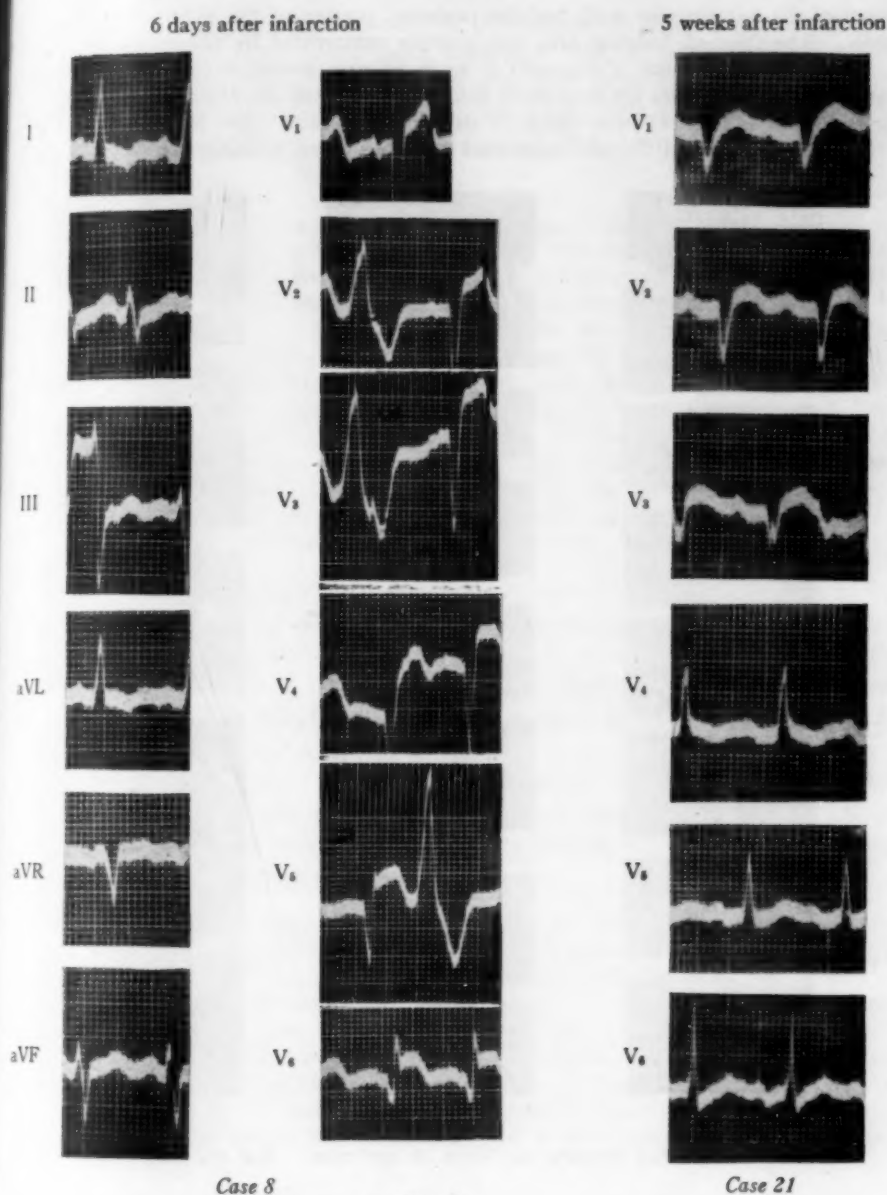
Case 9. The entire anterior wall of the left ventricle, including 1 cm. of the apical end of the posterior wall and the anterior half of the apical portion of the left side of the septum, was infarcted. The distal one-third of the anterior wall was thinned and bulging. In addition, there was recent, massive infarction of the posterior wall of the left ventricle, part of the posterior wall of the right ventricle, the

base of the left anterior wall, and the posterior portion of the septum from apex to base. The thinned, bulging area was sharply demarcated by fibrous tissue.

At another hospital, a diagnosis of acute anterior infarction had been established some 17 months before his final entry into the San Francisco Hospital. One electrocardiogram (figure 4) was taken 10 days before death. The large, abnormal Q_3, coved S–T$_3$, inverted T$_3$, and depressed S–T$_{1 and 2}$ were probably due to the recent
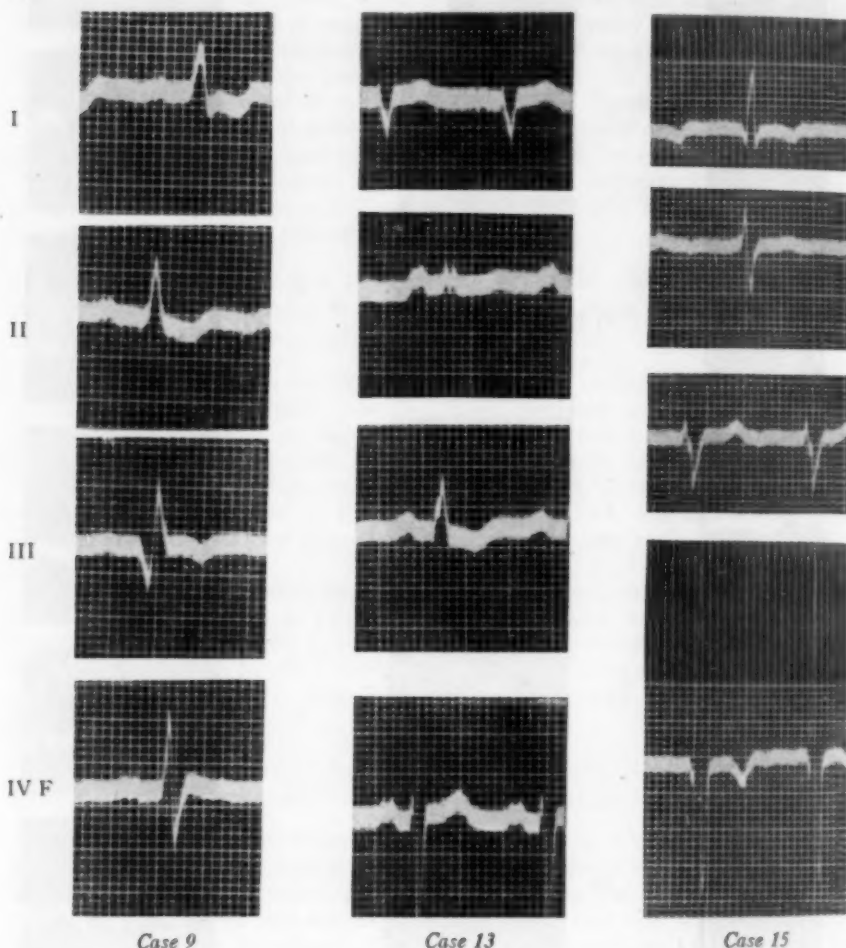
FIG. 4. Three cases showing no "signs of aneurysm." See text for explanation.

posterior infarct, although the effects of digitalis may also have played a part. Lead IV F shows no Q, an R of 8 mm. and an S of 5 mm. The S–T segment is slightly, if at all, elevated, and T is nearly flat in this lead.

In this case, the electromotive forces contributed by the left ventricle must have been practically nil. The initial upward deflection in IV F could have been caused by the action current approaching along the anterior basal

half of the septum, the apical, anterior portion of the right septum, and possibly the anterior wall of the right ventricle, and the later S wave, by the retreating innervation of the more remote portions of the right ventricle. The absence of S–T elevation over the aneurysm (IV F) was probably due to the inactivation of the major portion of the posterior wall of the left ventricle.

Case 13. There was a distinct outward bulge of the left anterior wall at the apex, which was 4 mm. in thickness and largely replaced by fibrous tissue. Some areas, however, were soft and suggested a superimposed recent infarct. In the mid-posterior wall of the left ventricle was a very thin, densely scarred area, 2 cm. in diameter and 3 mm. in thickness. There was also extensive, patchy discoloration and fibrosis throughout the rest of the left ventricle, anteriorly, posteriorly and septally. There was similar, but much less extensive, fibrosis of the right ventricle.

Electrocardiograms (figure 4) taken February 27, March 7 and May 3, 1946, were practically identical. The last infarct was calculated as having occurred on February 20. Autopsy was done on June 6. Lead IV F showed an R of 2.0 mm. and an S of about 15 mm. There was no Q wave. The T was upright. The S–T was elevated about 0.5 mm., if at all. The patient was on digitalis. There was rather marked right axis deviation.

In this case, as in case 9, though not to the same extent, there was rather widespread destruction of the left posterior wall, and the same explanation for the absence of Q and S–T elevation might apply here. Of course, the electrode for Lead IV F might not have been over the infarct, but it would have required gross misplacing to show no signs at all of this rather large infarct.

The relatively large S in IV F and the marked right axis favor the view that the right ventricle was the predominant one in this case. Rather amazingly, there was practically no hypertrophy of either ventricle, in spite of the presence of malignant hypertension.

Case 15. In the upper, lateral portion of the left ventricular wall was an area 4 cm. in diameter and 4 to 5 mm. in thickness, which bulged outward and was largely replaced by grayish, fibrous tissue. The rest of the ventricle was 11 to 12 mm. in thickness. A recanalized old thrombus was present 4.5 cm. from the ostium of the left circumflex artery. The heart weight was 720 gm.

Three electrocardiograms (figure 4), at weekly intervals shortly before death and about two years after infarction, were identical. Lead I showed an S–T that was isoelectric and coved, and a T that was inverted. Lead IV F showed a Q of 1.5 mm. which was narrow, an R of 34 mm. and an S of 15 mm.; coved but isoelectric S–T, and an inverted T.

The findings in Lead IV F were suggestive of left ventricular hypertrophy, which was decidedly present. The absence of criteria diagnostic of infarction in Lead IV F was undoubtedly due to the high lateral location of the infarct. A lateral location was suggested by Lead I.

Case 11. The anterolateral wall of the left ventricle showed a spherical bulging about 7 cm. in diameter, which projected 1 cm. out beyond the rest of the wall, was

largely replaced by fibrous tissue, and was 3 mm. in thickness. The left anterior descending artery was recanalized.

The only available electrocardiogram (figure 5) was taken when the patient was in the San Francisco Hospital 18 months previously, and some two months after the calculated clinical onset of infarction. Admittedly, the onset in this case was a bit indefinite, since the patient had no pain but, instead, an insidious onset of increasing dyspnea, edema and orthopnea. The electrocardiogram showed a Q, coving of S–T, and inversion of T in Lead I. Lead IV F showed QS complexes, an S–T elevation of 3 to 4 mm., coving of S–T, and late inversion of T.
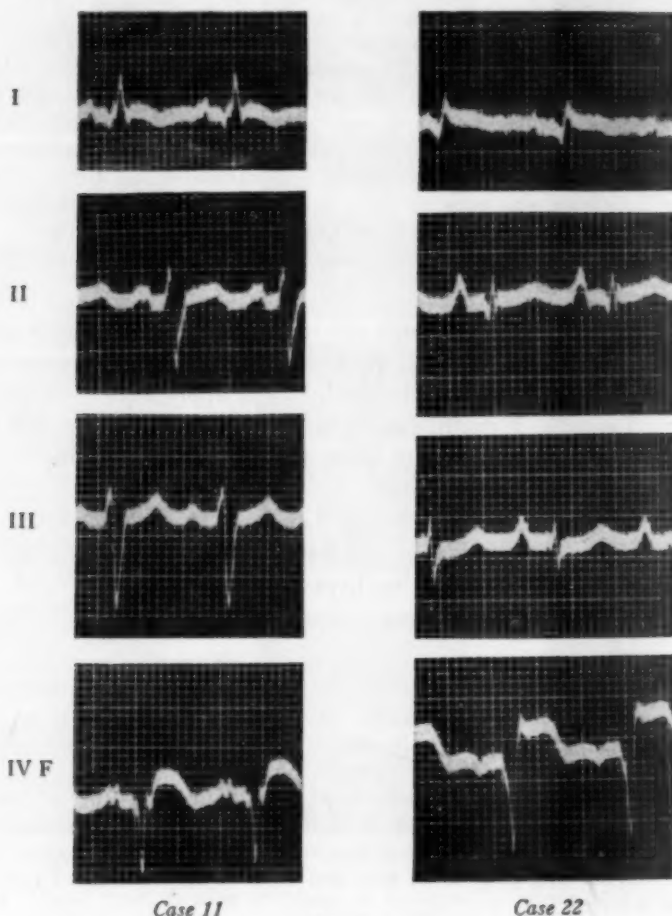
Case 11   Case 22
Fig. 5.

In this case, again, one sees QS complexes and S–T elevation over the aneurysm persisting beyond the usual "injury current" time.

Case 22. This patient had a typical attack of infarction on June 18. Autopsy on July 5 showed a bulging of the left anterior wall surmounting a 7 by 5 cm. infarct. The left wall was 20 mm. thick, except over the bulging area, where it was 3 mm. thick. The left anterior descending artery was plugged with a red, gray thrombus.

Electrocardiograms (figure 5) on June 29 and July 2 were practically identical. $Q_{1 \text{ and } 2}$ were prominent, $R_{1, 2 \text{ and } 3}$ were very small, S–T was elevated in Lead I and depressed in Lead III, and T_1 was beginning to turn down. In Lead IV F, S–T was elevated 4 to 4.5 mm., and T was diphasic $(+ -)$; Q was 9 to 10 mm. deep, and there was an R of 0.5 mm.

In this case, persistent S–T elevation is demonstrated 14 days after infarction. The complexes would be QS in type except for the tiniest of R waves. An electrode at the apex would probably have straddled the boundary between this aneurysm and the good muscle beyond, thus accounting for an R wave.

DISCUSSION

RS Complexes. Two of the cases presented here (9 and 13) showed RS complexes in Lead IV F. It seems practically out of the question that this electrode could have been placed so far off as to fail to record even a Q wave in the presence of such extensive infarcts. It is believed that the very extensive destruction of the posterior wall in case 13 and the almost complete destruction of the posterior wall in case 9 were responsible for the R-S patterns. It is believed that potentials on the right side of the septum, and possibly some of the anterior right wall, were responsible for the R waves and potentials over the rest of the right ventricle for the S waves in IV F. The relatively large S in this position, as well as an S in Lead I, is compatible with this explanation.

QRS or QR Complexes. Such complexes were registered in three cases (3, 15 and 22). In case 15 the aneurysm was high on the lateral wall and would almost certainly not have registered at the apex. In case 22, the R was very small compared to the deep Q, while in case 3 the R was large. In such cases it is very likely that the electrode was straddling the boundary between the dead and healthy myocardium. It is also possible that occasionally, even if an electrode is overlying a dead area, the potentials outside this area may not cancel themselves out entirely, so that a wave may approach the electrode unopposed and give rise to an R wave.

QS Complexes. These were present in the remaining five cases, and signify transmural involvement of the area being drained by the given electrode.

S–T Segment. This portion of the electrocardiogram was elevated for a time longer than usually seen from injury currents in seven of the 10 cases. As mentioned above, in one case the electrode was not over the aneurysm, and in the other two there was extensive destruction of the posterior wall. This is consistent with the theory that persistence of S–T elevation in aneurysm is due to remote potentials, chiefly from the posterior wall of the left ventricle. As far as contour is concerned, both upward concavity and convexity were seen in the S–T segments.

T Waves. T waves were upright, inverted or diphasic. When diphasic, however, they were always plus-minus, and never minus-plus.

Multiple Chest Leads.   It is regretted that more of these cases did not have multiple chest leads available.   As more cases are observed which have had such leads, the final solution of this problem will in all likelihood be forthcoming.   It is hoped that those who observe living cases will explore the region over the site of the aneurysm as determined by fluoroscopy to define further the electrocardiographic findings.

CONCLUSIONS

1. It is believed that QS complexes, together with persistent S–T elevation in one or more precordial leads, are strongly suggestive, if not actually diagnostic, of underlying ventricular aneurysm, true or potential, due to a previous infarction.   The T waves may be upright, inverted or diphasic, but if diphasic they are plus-minus.

2. Extensive destruction of the posterior wall of the left ventricle probably explains the absence of S–T elevation and the presence of RS complexes in some cases of aneurysm.

3. QR or QRS complexes with S–T elevation may result if the electrode is only partially over the dead area, or possibly occasionally may result from potentials outside the dead area, even though the electrode is centered over the aneurysm.

BIBLIOGRAPHY

1. Eliaser, M., Jr., and Konigsberg, J.: Electrocardiographic findings in cases of ventricular aneurysm, Arch. Int. Med. **64**: 493, 1939.
2. Nordenfelt, O.: Electrocardiogram in aneurysm of the heart, Acta med. Scandinav. 102: 101, 1939.
3. Crawford, J. H.: Aneurysm of the heart, Arch. Int. Med. **71**: 502, 1943.
4. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram, Am. Heart J. **27**: 19, 1944.
5. Thaon, M.: Étude électrocardiographique de cinq anéurysmes pariétaux du coeur, Arch. d. mal. du coeur **40**: 179–191 (May–June) 1947.
6. Myers, G. B., et al.: Correlation of electrocardiographic and pathological findings in large anterolateral infarcts, Am. Heart J. **36**: 838, 1948.
7. Rosenberg, B.: The electrocardiogram in ventricular aneurysm, Am. Heart J. 37: 267, 1949.

CASE REPORTS

FATAL APLASTIC ANEMIA DUE TO STREPTOMYCIN: CASE REPORT AND BRIEF REVIEW OF PERTINENT LITERATURE *

By C. Ray Womack, M.D., *Nashville, Tennessee*,† and Charles B. Reiner. M.D., *Philadelphia, Pennsylvania*

Streptomycin was first described over five years ago by Waksman and his coworkers.[21] As experience has accumulated regarding its clinical use, manifestations of toxicity have become increasingly and significantly apparent. Depression of the blood-forming organs has been, however, an uncommon occurrence, and only two previous cases of aplastic anemia due to streptomycin are known to have been reported at the time of this communication.

Little evidence of toxic effects of streptomycin administration upon the hematopoietic system has been observed in animal studies. Feldman and Hinshaw[10] noted no effect on hematopoietic tissues or hemoglobin values in tuberculous guinea pigs treated for 54 to 61 days with streptomycin. Molitor and associates,[17] in chronic toxicity experiments using mice, rats, guinea pigs, monkeys and dogs, found a slight anemia in monkeys only. This was most common in those animals treated 66 days. In monkeys and dogs, Mushett and Martland[19] found a slight, transient normocytic anemia without changes in the other formed elements of the blood. The marrows of these animals and of rats similarly treated revealed no abnormalities. The spleens occasionally showed some hemosiderin, a possible indication that the anemia was hemolytic in character. These observers concluded from animal experiments that the anemia associated with the administration of streptomycin was probably of no serious consequence, since it was transitory and no marrow involvement was demonstrated. Heilman,[11] using tissue culture technic, found streptomycin to have a low toxicity for wandering macrophages and leukocytes but a fairly high toxicity for fibroblasts.

In man evidence of low toxicity for the hematopoietic system has likewise been obtained.[6, 12, 27] Hettig and Adcock[13] report no evidence of erythropoietic suppression, hemolysis, leukopenia or abnormality of differential counts in their nine patients, some of whom received a total of 72 gm. of streptomycin over a period of 56 days. Madigan and colleagues,[16] in 14 cases treated with streptomycin varying in dosage from 0.4 gm. in nine hours to 108 gm. in 90 days, noted no abnormalities of the blood. DeBakey and Pulaski,[6] in a review of 706 Army cases treated with the agent, noted no depression of marrow elements. Nichols and Herrell,[20] reporting the treatment of 192 patients with streptomycin in dosage varying from 1 to 3 gm. daily, do not mention evidence of bone marrow depression

in their description of toxic effects.   In a report by the National Research Council [4] of the treatment of 1,000 individuals with the antibiotic, no mention is made of disturbances in the blood-forming organs, and none is reported by Anderson and Jewell.[2]

It has been reported, however, that in two instances thrombocytopenia occurred in patients with acute brucellosis who received 6 gm. of the drug daily.[1, 24] In one case it is noted that the drug had been given for a few days; in the other, the length of administration is not mentioned.   It is possible that these two reports describe the same patient.   McDermott [15] has noted that leukopenia (1,500 to 3,000 cells), occasionally accompanied by relative granulocytopenia, occurs at times during streptomycin therapy of tuberculosis, usually in persons with hematogenous tuberculosis in which involvement of the bone marrow is not uncommon.   Despite continuance of therapy, the counts returned to normal in all instances.   However, he recommended that, in the absence of hematogenous tuberculosis, leukopenia be considered a toxic manifestation and the drug be discontinued.   Farrington and associates [9] noted no anemia or thrombocytopenia in 16 subjects receiving 3 gm. daily for from 93 to 120 days.   Two patients developed leukopenia without granulocytopenia in conjunction with a drug sensitivity reaction, and a third developed leukopenia (2,000 to 3,000 cells) with a relative granulocytopenia in the second month of therapy.   These changes lasted 60 days and disappeared spontaneously during continuance of streptomycin treatment.   The patient had acute hematogenous tuberculosis at the onset of therapy and was a radiologist whose leukocyte counts had "always been very low." Mordasini [18] reports that, among 17 cases treated with streptomycin, hepatomegaly and a severe anemia appeared in one patient with acute miliary tuberculosis.   No further descriptive comment is made.   Bunn,[2] discussing toxic manifestations among 650 patients with various types of streptomycin-treated tuberculosis, reports two instances of bone marrow depression developing during prolonged therapy.   One of these was noted to be a Veterans Administration case.   These patients apparently did not die, and the author states that the complication is so rare that mere mention of its possibility is sufficient, especially since the "depression is not permanent."   Of 900 patients treated with streptomycin in Veterans Administration, Army and Navy hospitals, there were eight instances (0.98 per cent) of blood dyscrasias in the group.[5, 28]   Five of these patients developed relatively mild leukopenia with neutropenia.   Three developed agranulocytosis and, of these, one had generalized miliary tuberculosis.   Cessation of streptomycin was followed by return of normal bone marrow function, despite progression of their disease.   Bunn's patient in a Veterans Administration hospital may possibly be included among these eight cases.

In 1948, Deyke and Wallace [7] reported that two patients developed aplastic anemia among 400 cases of tuberculosis treated with streptomycin in an Army hospital.   These may be the same patients mentioned by Bunn.   One patient, after receiving 2 gm. of the drug daily for 79 days, died 19 days later despite discontinuance of the agent.   The postmortem examination confirmed the clinical impression of an aplastic anemia.   The other patient received 2 gm. of streptomycin daily for 95 days and, although the drug had been discontinued, was deteriorating at the time of the report and was not expected to survive.   A sternal aspiration revealed diminution in the young red and white cell forms of the mar-

CASE REPORT

A 76 year old white male was admitted to the hospital on May 18, 1947, complaining of hoarseness of five weeks' duration. His illness began two months prior to admission, when he had "the grippe." Three weeks later he became hoarse. He was advised to refrain from using his voice for a few weeks, but there was no improvement. He had lost 18 pounds in weight during the year prior to admission and attributed this to anorexia and edentia. There had been occasional slightly productive cough and intermittent ankle edema related to the erect posture, but no fever, sputum or hemoptysis. There was no history of bleeding tendency or blood dyscrasia.

His temperature was 100° F. and pulse rate 80 per minute. He was a well-developed, pale and poorly nourished man whose voice was a hoarse whisper. The vocal cords were mammillated, thickened and edematous, and bled easily. Lymph nodes were normal. The chest was emphysematous, and scattered fine crackling râles were heard throughout the lungs. The heart seemed normal. The blood pressure was 105/60 mm. of mercury. The liver and spleen were not palpable. There was evidence of generalized hypertrophic arthritis. Varicose veins of the legs were present bilaterally. The reflexes were normal.

The red blood cell count was 4.23 million per cu. mm., with a hemoglobin of 13.6 gm. per cent. The white blood cell count was 7,000 per cu. mm., with 58 per cent neutrophils, 41 per cent lymphocytes, and 1 per cent eosinophils. The sedimentation rate was 34 mm. per hour (Wintrobe). Coagulation and bleeding times were normal. The Kahn serologic test for syphilis was negative. The urine was normal except for an occasional 1 to 2 plus albuminuria. Roentgen-ray examination of the chest revealed the presence of extensive, far-advanced, fibrocalcific tuberculosis with emphysema, and repeated examinations during the patient's hospital course showed no significant change. A first strength Mantoux test (P. P. D.) was positive at 48 hours. Examinations of the sputum and gastric washings revealed acid-fast bacilli, which proved to be tubercle bacilli by culture and guinea pig inoculation.

A low grade fever persisted, with sporadic temperature elevations to 100 to 101° F. By July 7, 1947, there had been no improvement in his condition. The administration of streptomycin hydrochloride was begun. He received 0.2 gm. every four hours intramuscularly, and 0.1 gm. by aerosol every three hours six times daily. Nine days later a fiery red macular rash developed and subsided spontaneously within one day. It was thought by a consulting dermatologist to be caused by streptomycin. Intermittent ankle edema appeared after July 29 and was associated with enlargement of the heart by roentgen-ray examination and with the development of a reddish-brown, symmetrical, scaling dermatitis of the hands, wrists, feet and ankles. During the administration of thiamine hydrochloride and nicotinamide the edema subsided, the heart size returned to normal and the skin rash improved, leaving some pigmentation. Residual edema was believed to be related to his varicosities. These changes were felt to be manifestations of beri-beri and pellagra, especially in view of the patient's response to thiamine and nicotinamide. At no time did he show clinical or laboratory evidence of congestive cardiac failure. The serum proteins and A/G ratio, icteric index, prothrombin time, bromsulfalein retention, thymol turbidity and cephalin flocculation tests of liver function were repeatedly normal. A needle biopsy revealed normal liver tissue. There was no evidence of azotemia at any time, but the urea clearance test was 57 per cent of average normal.

On streptomycin therapy the larynx gradually showed striking improvement, and

by September, 1947, he was able to talk clearly though not perfectly. Tubercle bacilli could not be demonstrated by smear or guinea pig inoculation after August, 1947. Early in October, slight vertigo and some unsteadiness of gait were noted. These were considered to be toxic manifestations of streptomycin on the vestibular apparatus but, because of his marked symptomatic laryngeal improvement and improvement in the appearance of the larynx, the drug was not discontinued. The symptoms of toxicity persisted but did not progress.

On October 8, 1947, the red blood count was 3.65 million per cu. mm., with 11.5 gm. of hemoglobin, and the white blood count was 4,000 per cu. mm., with 65 per cent neutrophils, 29 per cent lymphocytes, and 6 per cent eosinophils. One week later he lost his appetite but was able to eat and retain food. On October 22, after he had received 129.6 gm. of streptomycin by injection and approximately 64.8 gm.
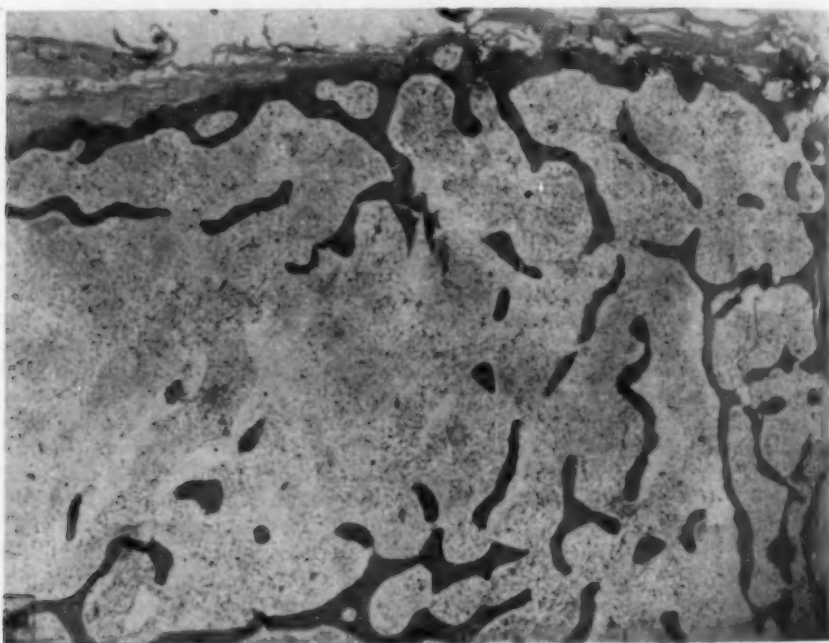

Fig. 1. Cross section of sternum. Normal bone trabeculae surrounded by fatty marrow containing few myeloid elements. H and E (15 ×).

by inhalation over a period of 106 days (total: 194.4 gm.), he suddenly complained of severe nausea, vomited about 500 c.c. of grossly bloody material, became very dyspneic, cold and clammy, and appeared to be in peripheral vascular collapse. The blood pressure was 85/40 mm. of mercury. A few petechiae were present on the ankles. There were increased tendon reflexes on the left, a partially sustained ankle clonus, and a left Hoffman and Babinski sign. Although he was conscious, these signs were felt to suggest an intracranial vascular accident. No clear-cut muscle weakness was evident. A portable chest roentgenogram showed no change. An electrocardiogram showed depressed S–T segments in all leads and occasional premature ventricular beats. The red blood count was 1.18 million per cu. mm., with 4.3 gm. of hemoglobin. The white blood count was 2,700 per cu. mm., with 1 per cent neutrophils and 99 per cent lymphocytes. Platelets were almost absent from

the blood smear, but the platelet count was 53,000 per cu. mm. He was given intra-
venous plasma but rapidly died before matched blood was available, about one hour
following the onset of the terminal episode.

   Autopsy Report*: Calcified nodules about 1 cm. in diameter, containing caseous
material and acid-fast bacilli, were present in the right and left upper pulmonary
lobes. There was no other evidence of pulmonary tuberculosis. Many petechiae
were present above the false vocal cords. The true cords were fibrotic and con-
tracted, and the mucosal surface was white and opaque. Typical tubercles were
present in the submucosa. A few subepicardial petechiae were present. The cor-
onary arteries showed atheromatous plaques. The myocardium appeared normal,
but microscopically the myocardial fibers were separated by edema fluid and some
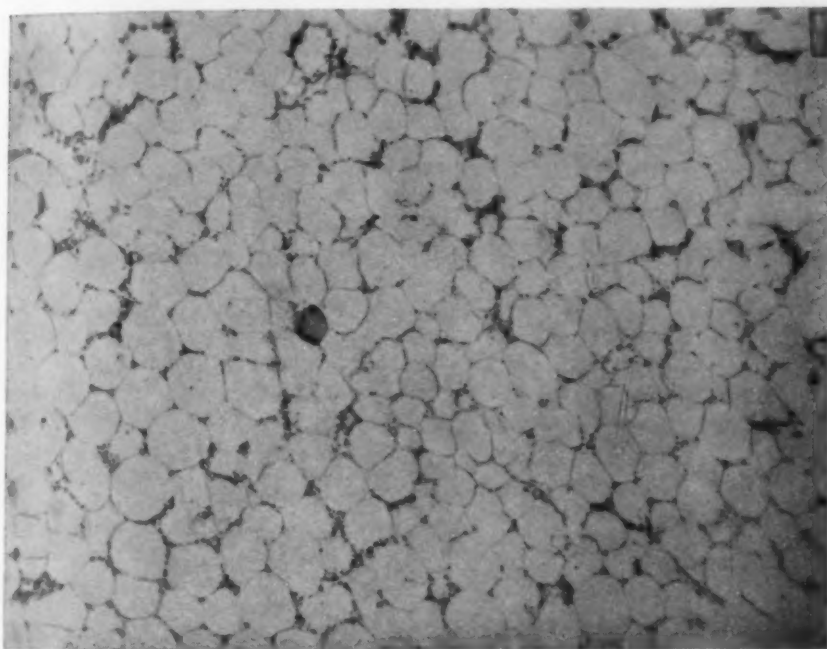fatty infiltration and fragmentation of muscle fibers were present. The stomach was

Fig. 2. Sternal bone marrow. Scattered areas of hematopoietic tissue among fat cells.
H and E (100 ×).

dilated and filled with chocolate-colored bloody fluid, and similar material was present
throughout the gastrointestinal tract. Numerous petechiae were present in the
mucosa of the stomach, and an area of purpura, 1 by 6.5 cm., was present in the
colon 30 cm. from the anus. Microscopically, the stomach and intestines showed no
significant findings except for dilatation of the blood vessels in the small bowel and
small areas of hemorrhage. A small, well-differentiated, ulcerating adenocarcinoma,
extending into the muscular coat, was present 15 cm. above the anus. No metastases
were evident. The kidneys appeared grossly normal but showed a few small, well-
healed infarcts due to arteriosclerotic occlusion of small arteries. The thyroid,
gall bladder, liver, spleen, pancreas, adrenals, prostate, bladder and skeletal muscle

---

* The autopsy was performed by Philip T. Flynn, Captain, M. C., A. U. S.

showed no significant abnormalities, grossly or microscopically. Except for athero-matous changes in some of the basilar arteries, the brain was normal. There was no evidence of intracranial bleeding. The right femur showed extremely yellow fatty marrow. The marrow in the ribs and vertebrae was very pale. Microscopi-cally there was everywhere a severe aplasia of the marrow elements, with a few islands of hematopoietic tissue remaining (figures 1 and 2). Only a rare myeloid form was found, and a few normoblasts persisted in the form of small foci. Several larger islands were evident, consisting mainly of normoblasts, lymphocytes, and an occasional myelocyte and myeloblast, surrounded by a relatively clear zone which was in turn surrounded by a secondary ring of cells, mainly normoblasts, with a few eosinophils and lymphocytes (figure 3). These were interpreted as being possible attempts at regeneration. There was no evidence of tuberculous infection in the
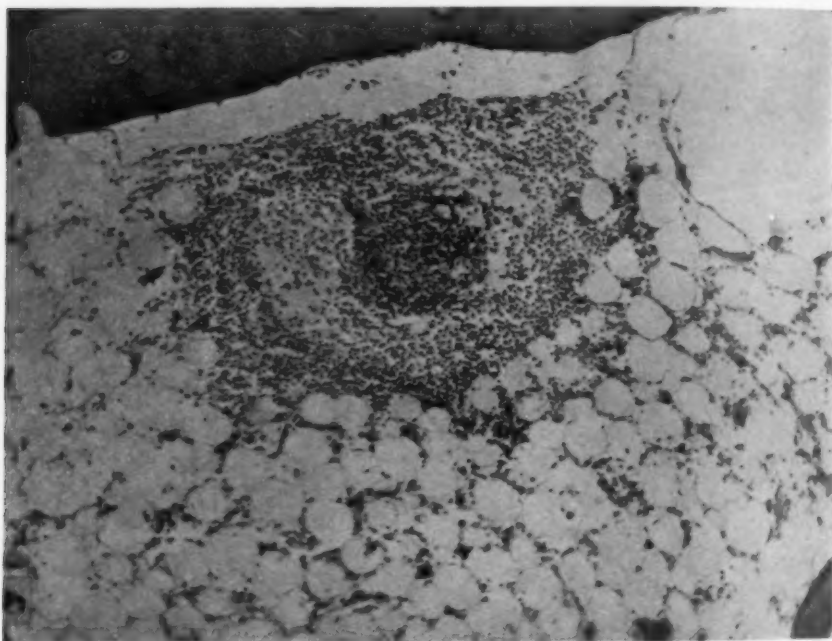

Fig. 3. Sternal bone marrow. Island of hematopoietic tissue in fatty and relatively aplastic marrow. H and E (200 ×).

marrow. The picture microscopically was considered to be typical of that seen in aplastic anemia.

DISCUSSION

There seems to be little doubt that this patient developed an acute, progres-sive depression of the hematopoietic system as a result of long-continued strepto-mycin therapy of laryngeal and pulmonary tuberculosis. He received no other medication, except for thiamine hydrochloride, nicotinamide, occasional small doses of aspirin (0.6 gm.) for joint pains related to his hypertrophic arthritis, and rare doses of sodium pentobarbital (0.1 gm.), with none of which had he pre-viously shown any evidence of toxicity. There was no evidence clinically or

pathologically of acute disseminated tuberculosis. The fatal hemorrhage causing the patient's death was believed to be due to thrombocytopenia. The final platelet count is regarded as a laboratory error, in view of the blood smear and marrow findings. The suspected intracranial bleeding was not confirmed by necropsy, and the neurologic signs were most likely the result of cerebral arteriosclerosis and the acutely developing severe anemia. The final blood counts were undoubtedly contributed to by the gastrointestinal hemorrhage, but the morphology of the bone marrow made a diagnosis of aplastic anemia appear certain.

The blood counts noted on October 8 probably should have served as a warning of the events to come, but their significance was not realized at the time. In view of a previous report of aplastic anemia,[7] it is doubtful whether discontinuance of the drug would have prevented the patient's death. The terminal eosinophilia was of interest. Eosinophilia of 5 per cent or greater has been noted in nine of 11 patients treated with streptomycin, and in five of these it appeared during the second month of therapy.[4] In addition, 14 of 16 subjects given 3 gm. per day for 120 days showed eosinophilia.[9] Two of these had a transient leukopenia (3,000 to 4,000 cells) without granulocytopenia.

It is remarkable that manifestations of thiamine and niacin deficiency appeared in this patient despite an apparently adequate vitamin intake, a high-caloric high-vitamin diet having been supplemented daily by six commercial multivitamin tablets. These manifestations responded to further increase in the dosage of thiamine (parenteral) and niacinamide. One might speculate that enough streptomycin administered by aerosol might be swallowed to interfere with intestinal synthesis of niacin in a manner similar to that exhibited by phthalylsulfathiazole in rats,[25] or that streptomycin may directly or indirectly exert an antivitamin or anti-enzyme effect in a manner analogous to that of known pellagragens and antithiamines.[8, 14, 26] Whatever the mechanism producing these deficiencies, moderately large supplements of thiamine and nicotinamide were required to relieve them and improvement was relatively slow. One can only conjecture as to whether a similarly developing, but as yet unclarified, deficiency state might be implicated in the depression of hematopoiesis.

In spite of the rarity of hematologic disturbances in patients treated with streptomycin, it would appear wise to make frequent periodic examinations of the blood cells, especially in patients treated over a prolonged period with more than 1 gm. per day of the drug.

SUMMARY

1. A case is presented in which a fatal aplastic anemia with granulocytopenia and thrombocytopenia developed during streptomycin therapy of laryngeal and pulmonary tuberculosis, the patient's death resulting from gastrointestinal bleeding.

2. This is the third reported case of this complication of streptomycin therapy.

3. Some of the pertinent literature is briefly considered.

BIBLIOGRAPHY

1. Adcock, J.: Personal communication to McDermott.[15]

2. Anderson, D. G., and Jewell, M.: The absorption, excretion and toxicity of streptomycin in man, New England J. Med. 233: 485–491, 1945.

3. Bunn, P. A.: Streptomycin in the treatment of human tuberculosis, Dis. Chest 14: 670–681, 1948.

4. Council on Chemotherapeutics and Other Agents, N. R. C.: Streptomycin in the treatment of infections. A report of 1000 cases, J. A. M. A. 132: 70–77, 1946.

5. Council on Pharmacy and Chemistry, A. M. A.: The effects of streptomycin on tuberculosis in man. Preliminary statement, J. A. M. A. 135: 634–641, 1947.

6. DeBakey, M. E., and Pulaski, E. J.: An analysis of the experience with streptomycin therapy in United States Army hospitals, Surgery 20: 749–760, 1946.

7. Deyke, V. F., and Wallace, J. B.: Development of aplastic anemia during the use of streptomycin. Report of two cases, J. A. M. A. 136: 1098, 1948.

8. Editorial: Antivitamin activity of related compounds, J. A. M. A. 134: 1550, 1947.

9. Farrington, R. F., Hull-Smith, H., Bunn, P. A., and McDermott, W.: Streptomycin toxicity. Reactions to highly purified drug on long-continued administration to human subjects, J. A. M. A. 134: 679–688, 1947.

10. Feldman, W. H., and Hinshaw, H. C.: Effect of streptomycin on experimental tuberculosis in guinea pigs: a preliminary report, Proc. Staff Meet., Mayo Clin. 19: 593–599, 1944.

11. Heilman, D. H.: Cytotoxicity of streptomycin and streptothricin, Proc. Soc. Exper. Biol. and Med. 60: 365–367, 1945.

12. Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Herrell, W. E.: Streptomycin: absorption, diffusion, excretion and toxicity, Am. J. M. Sc. 210: 576–584, 1945.

13. Hettig, R. A., and Adcock, J. D.: Studies on the toxicity of streptomycin for man: a preliminary report, Science 103: 355–357, 1946.

14. Krehl, W. A., Sarma, P. S., Teply, L. J., and Elvehjem, C. A.: Factors affecting the dietary niacin and tryptophane requirement of the growing rat, J. Nutrition 31: 85–106, 1946.

15. McDermott, W.: Toxicity of streptomycin, Am. J. Med. 2: 491–500, 1947.

16. Madigan, D. G., Swift, P. N., and Brownlee, G.: Clinical and pharmacological aspects of the toxicity of streptomycin, Lancet 1: 9–11, 1947.

17. Molitor, H., Graessle, O. E., Kuna, S., Mushett, C. W., and Silber, R. H.: Some toxicological and pharmacological properties of streptomycin, J. Pharmacol. and Exper. Therap. 86: 151–173, 1946.

18. Mordasini, E.: Streptomycin and tuberculosis—a short review, Tubercle 29: 49–57, 1948.

19. Mushett, C. W., and Martland, H. S.: Pathologic changes resulting from the administration of streptomycin, Arch. Path. 42: 619–629, 1946.

20. Nichols, D. R., and Herrell, W. E.: Streptomycin. Its clinical uses and limitations, J. A. M. A. 132: 200–205, 1946.

21. Schatz, A., Bugie, E., and Waksman, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria, Proc. Soc. Exper. Biol. and Med. 55: 66–69, 1944.

22. Streptomycin Committee, V. A. Central Office: The effect of streptomycin upon pulmonary tuberculosis in man—Preliminary report of a cooperative study of 223 cases by the Army, Navy and Veterans Administration, Vet. Admin. Tech. Bull. (TB 10–37), Sept. 24, 1947.

23. Streptomycin Committee, V. A. Central Office: A preliminary statement concerning the effects of streptomycin upon tuberculosis in man, Vet. Admin. Tech. Bull. (TB 10–34), Aug. 5, 1947.

24. Sturgis, C. C., in discussion of Keefer et al., Tr. A. Am. Physicians 59: 206–219, 1946.

25. Tepley, L. J., Krehl, W. A., and Elvehjem, C. A.: Intestinal synthesis of niacin and folic acid in the rat, Am. J. Physiol. 168: 91–97, 1947.

26. Woolley, D. W.: Recent advances in the study of biological competition between structurally related compounds, Physiol. Rev. **27**: 308–333, 1947.

27. Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. M., and Rhoads, J. E.: Studies on streptomycin in man. I. Absorption, distribution, excretion and toxicity, Am. J. M. Sc. **210**: 421–430, 1945.

PORPHYRIA: CLINICAL OBSERVATIONS AND A FAMILY VIGNETTE *

By George L. Calvy,† Cdr. MC, U. S. Navy, *Newport, Rhode Island*, E. J. Jaruszewski,‡ Cdr. MC, U. S. Navy, *Philadelphia, Pennsylvania*, and H. H. Carroll, F.A.C.P., Capt., MC, U. S. Navy, *San Francisco, California*

Porphyria presents a varied clinical picture of abdominovisceral, neurologic and cutaneous involvement in association with increased excretion of porphyrins in the urine and feces. The diagnosis is to be entertained whenever passage of dark, red or mahogany colored urine is cited in a history, especially with colicky abdominal pain and constipation, obscure neurologic changes, or photosensitivity of the skin. While the disease is generally considered to be rare in this country, Waldenström's [2] family studies in Sweden indicate that it occurs not infrequently in that country, or at least to such an extent that individuals manifesting undue "nervousness" or hysterical behavior are often studied for evidence of porphyria. An increasing number of case reports indicates growing awareness among clinicians of this metabolic disorder.[1-3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]

Continuing contributions, especially from Watson and his co-workers at Minnesota and from the Mayo team of Brunsting, Mason and Aldrich, are providing a clearer picture of this hitherto obscure disease.

The present report describes a family in which eight cases occurred, and adds further evidence for Garrod's postulate that porphyria is due to an "inborn error" of metabolism and is often familial in distribution.[3]

Case Report

A 20 year old white male was admitted to a naval dispensary on February 27, 1948, with the complaint, "My face burns and itches." He was given Benadryl, 50 mg. every four hours. The burning sensation increased and periorbital edema appeared. Benadryl was discontinued after the second day.

Physical examination revealed marked edema of the periorbital tissues and the cheeks. The temperature was 38° C. No other abnormalities were noted. The

patient became asymptomatic shortly after admission.   It was observed that his urine had a dark amber color, but tests for bile were negative.   He was transferred to the U. S. Naval Hospital, Great Lakes, Illinois, on March 2, 1948.

The patient had no complaints at the time of transfer.   He stated that since the age of 14 he had passed dark urine periodically.   Other than the use of "liver pills" for repeated episodes of constipation, he had not habitually used drugs, and he denied the use of barbiturates.   His parents described his early life experiences.   His weight at birth was three pounds and he was a "blue baby," cyanosis persisting for six weeks. Measles, mumps and chickenpox were his childhood diseases.   Allergy was denied. He enjoyed good health and development until the age of 14, when there was a
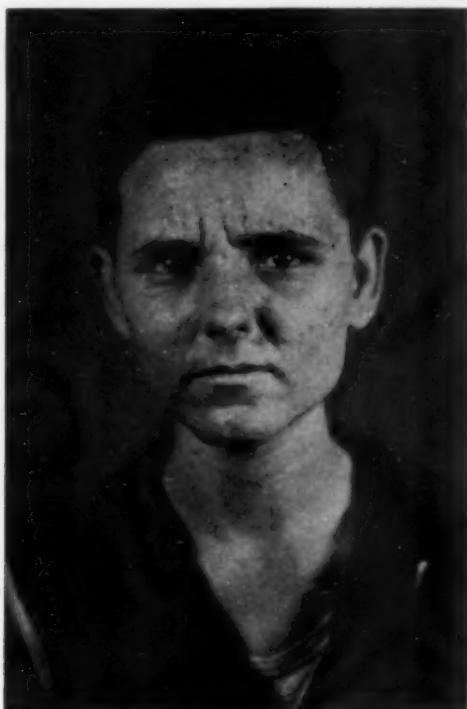

FIG. 1.   Index case, 20 year old seaman.

gradual onset of weakness, weight loss and lack of ambition.   Maximum weight prior to this time was 152 pounds.   A minimum of 99 pounds was later recorded. The diagnoses of malaria, anemia and avitaminosis were proposed at various times, and his parents treated him with quinine, vitamins and proprietary remedies.   A weight gain occurred, the symptoms diminished, and he enlisted in the Navy in December, 1947.   He was sent to a recruit training center where he underwent the rigorous conditioning experienced by all inductees, but he could not maintain the pace, tired easily, and soon appeared at sick bay.   At that time he weighed 105 pounds.

In the past he had learned to avoid work that involved exposure to the sun and sought inside employment.   At one time he worked as an auto mechanic but was obliged to give up this job, being unable to endure even mild trauma to his hands;

he said: "My hands blistered, festered and pained me." In general, declines in well-being coincided directly with outdoor activities and exposure to the sun.

Physical Examination: The patient was a small, 20 year old white male of gracile structure who appeared much older than his stated age (figure 1). His voice was restrained and high pitched, and his general mannerisms betrayed a lack of dynamic forcefulness. Temperature, pulse and respirations were normal. The blood pressure in each arm was 100 mm. Hg systolic and 60 mm. diastolic. The skin was grayish-brown in color, the alteration in color being most intense over the hands, face and neck. The skin over the interphalangeal joints of both hands was deeply pigmented; some areas on the dorsum of the hands appeared to be depigmented, and the skin was atrophic at these sites. There were excoriations and scarring on the face, arms and hands. The mucous membranes were normal in appearance. There were no cutaneous changes noted on the feet. A peculiar brownish pigmentation of the teeth was noted. The external ears did not manifest this sign.

Examination of the cardiovascular, respiratory, neurologic and genitourinary systems revealed only atrophic testes. Roentgenograms of the skull, serologic tests (Kahn), and studies of the cerebrospinal fluid disclosed nothing abnormal.

Clinical Course: On the eleventh day (March 8), the patient experienced nausea and cramping abdominal pain, and vomited several times. On the following day his condition became progressively worse and was considered critical. Jaundice was manifest. A urine specimen was reddish-brown in color and turned a dark coffee-color after exposure to sunlight, but porphobilinogen was not detected by the Watson-Schwartz qualitative test.[1d] The specimen was positive for bile. From the thirteenth to the twenty-third days there was a progressive increase in jaundice. The liver enlarged until it was palpable three fingerbreadths below the costal margin. Throughout this period the patient suffered considerable distress, vomiting frequently and complaining of severe upper abdominal pain. Neither chills nor sweats were observed during the foregoing period, and the highest temperature recorded did not exceed 38° C. He was maintained on parenteral fluids under a regimen designed to combat electrolyte imbalance by introduction of glucose, saline and lactate-Ringer solutions. Pain was obtunded by Demerol, 50–100 mg. at four to six hour intervals. Obstipation was extreme and was only slightly relieved by enemas and large doses of magnesium sulfate. The stools were in the form of hard pellets, normally pigmented.

The pattern of urinary output was unusual and showed a rhythmic variation in which a low 24-hour output, 500 to 650 ml., for four to five days was followed by a normal 24-hour output of 1,200 to 1,800 ml. for one to two days. This pattern persisted throughout the greater part of the period of hospitalization. Specific gravity varied from 1.010 to 1.028.

Laboratory findings were as follows: serum bilirubin, 25 mg./100 ml., cephalin flocculation test, 3 plus; total proteins (serum), 6.10 gm./100 ml. (albumin, 2.85 gm./100 ml., globulin, 3.25 gm./100 ml.); A/G ratio, .88; alkaline phosphatase, 2.12 Bodansky units. Erythrocyte fragility was normal. Blood smears showed no malarial parasites; no spherocytes were observed. Urinary urobilinogen was absent during the height of the visceral crisis. Urinalyses were negative for the presence of blood, casts, albumin and sugar.

Subjective improvement was apparent on the twenty-fourth day, although jaundice remained intense. On March 26 the cephalin flocculation test was 4 plus. A roentgenogram of the abdomen was normal in appearance. A urine specimen passed on this day turned black on exposure to sunlight. Porphobilinogen was absent. An episode of severe abdominal pain occurred but no increase in jaundice was noted. From this time on the jaundice rapidly faded, the patient's appetite improved, and a 25 pound weight gain was recorded.

During this period of apparent remission, porphobilinogen was first detected in the urine and was present thereafter. Another attack of severe abdominal pain and obstipation occurred on April 15 and lasted for two days, unaccompanied by jaundice.

Five weeks later, on May 20, bullous lesions were first noted on the hands 12 hours following exposure to ultra-violet light. (Subsequent reëxposures failed to reproduce these lesions.) On three occasions, following prolonged exposure to the summer sun (July and August), similar lesions appeared on the hands (figure 2).

Fig. 2. Appearance of hands following solar exposure. Note bullae, scarring and pigmentation.

Fluorescence was observed at the gingival borders on exposure under Wood's lamp. but this phenomenon disappeared with removal of detritus.

During the last three months of observation, prior to discharge from the naval service, the patient was free from abdominal distress and became a useful ward member. It was noted that loss of sleep or exposure to the sun was invariably followed by color changes in his urine ranging from pink to black. At no time did he refer to the pedigree of porphyria in his family, but he freely recited the socio-environmental difficulties of his brothers and their repeated failures of adjustment.

Additional Data: The Robinson-Kepler-Power water test was negative on two occasions; the glucose tolerance test was within the normal range. The electrocardiogram disclosed no abnormalities of the S–T segment or T waves.[13] The cerebrospinal fluid was normal. The A/G ratio rose to 1.2 as the serum albumin fraction increased. Other laboratory results were as follows: blood cholesterol, 285 mg./100 ml.; blood chlorides, 560 mg./100 ml.; prothrombin time, 100 per cent of normal. Erythrocyte. leukocyte and hemoglobin determinations did not reveal significant changes throughout the clinical course, typical findings being: erythrocyte count, 4,940,000 cu. mm.:

leukocyte count, 5,000 cu. mm.; hemoglobin, 14 gm./100 ml. Differential leukocyte counts were not noteworthy.

Porphyrin Determinations: A urine specimen obtained on July 25 was positive for porphobilinogen and contained uroporphyrin, 252 gamma/100 ml., and coproporphyrin, 620 gamma/100 ml. Another urine specimen obtained on July 27 contained uroporphyrin, 427 gamma/100 ml., and coproporphyrin, 500 gamma/100 ml. The test for porphobilinogen was positive. A specimen of feces obtained on this same day yielded uroporphyrin, 5,000 gamma/100 gm., and coproporphyrin, 1850 gamma/100 gm. The isomer was predominantly Type I in urine and stool assays for both uroporphyrin and coproporphyrin.

A Pedigree of Porphyria

The family background was investigated and evidence obtained that dark urine and other accompaniments of porphyria were present among its members (figure 3). In addition to the index case (H), seven others were known to possess stigmata of the disease (table 1).
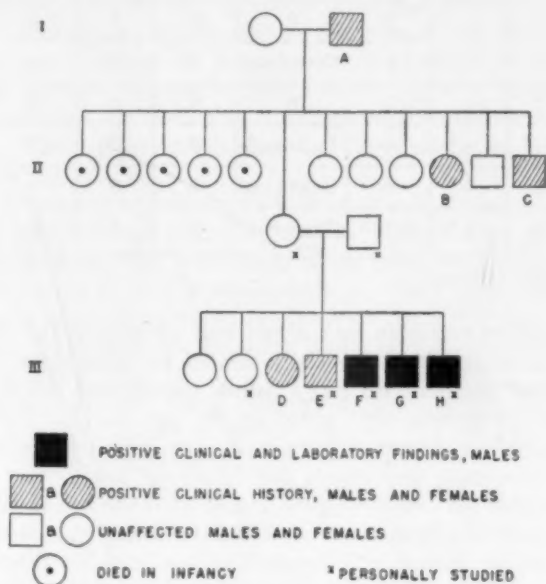

FIG. 3. A pedigree of porphyria.

The maternal grandfather (A) had periodic passage of reddish colored urine and "knew the sun didn't agree with him." At harvest time his hands blistered unless protected from the sun. He lived to the age of 65, his demise being attributed to apoplexy. His wife bore 12 children, five of whom died soon after birth. A daughter (B) exhibited the same signs as her father and was treated for hypertension. A son (C) had a similar history and died at the age of 54 of coronary thrombosis. Another daughter was committed to a mental hospital, but gross evidence of porphyria was denied by family members. A postpartum maniacal outburst occasioned her commitment. When she was interviewed, her

blood pressure was recorded as 220 mm. Hg systolic and 120 mm. diastolic in each arm.

The present generation of seven children contains four males and a female who have passed dark or red urine and have suffered cutaneous involvement (except H) to a mild degree. The female (D) experienced recurrent attacks of colicky abdominal pain as well as convulsive seizures and suffered from severe asthma. Her death at 17 followed extensive abdominal surgery for "appendicitis and complications."

TABLE I

Clinical Findings in Family Study

Gener-ation	Case	Age at Onset	Dark or Red Urine	Light Sensitiv-ity	C.N.S. In-volvement	Hyper-tension	G. I. Crises	Consti-pation	Jaundice	Aggra-vation by Alcohol
I	A♂	?	+	+++	0	+	?	?	0	?
II	B♀	15	+	++	0	+	0	?	0	0
	C♂	?	+	?	0	+	0	+	0	?
III	D♀	12	+	+	Grand mal	?	+	+	0	0
	E♂	17	+	0	0	0	0	+	0	+
	F♂	17	+*	+	Petit mal	0	0	+	0	+
	G♂	17	+*	+	Grand mal	0	0	+	0	+
	H♂	14	+*	+++	"Nervous"	0	+	+	+	+

* Porphobilinogen positive.

The four brothers resemble each other, and all have noted the phenomenon of dark or red urine and have especially related its appearance to alcoholic excesses. The eldest brother (E) has a sallow complexion but denies cutaneous involvement; red urine was first noted at the age of 17. The second eldest brother (F) recited a similar history that also included spells of weakness, "nervousness," numbness, paresthesia and "blacking out."

The third brother (G) enjoyed good health until the age of 17, at which time he suffered the first of a long series of convulsive seizures. It was at this time that he began to use alcohol, and inevitably associated his illness with its use. He is now a church member and an abstainer, and has suffered fewer convulsive attacks. Porphobilinogen was found in the urine specimens of F and G.

The family group was rural in origin and its dietary history was not abnormal. Consanguinity was denied. The father of the third generation remarked that constipation was one of the principal problems of his children, and added: "Never seen anything like it." He was concerned with the drinking habits of his sons, all of whom drank to excess, and he attributed their ill health to alcohol.

PORPHYRIA AND PORPHYRINURIA

The term "porphyria" is ordinarily applied to a state of metabolic dysfunction in which there is excretion of uroporphyrin (and coproporphyrin) in the urine

and feces. It is distinct from symptomatic or "secondary" porphyrinuria, wherein large amounts of coproporphyrin Types I and III may be excreted in the urine as the result of hepatic disease, heavy metal intoxication, or the use of sulfonamides, and other chemotherapeutic agents. Small amounts of coproporphyrin (10 to 320 μg. daily) are normally excreted in the urine and feces.[1c]

The production of porphyrins parallels hematopoietic activity and hemoglobin synthesis; tracer studies employing radioactive substances have confirmed this relationship.[25] Porphyrins * are components of tissue cells in both plants and animals and are essential elements of the respiratory pigments catalase, peroxidase, the cytochromes, chlorophyll, hemoglobin and myoglobin. A comprehensive review of the biochemical features of the porphyrins is contained in the reports of Waldenström,[2] Watson,[1c] Dobriner and Rhoads,[24] and Welcker.[27]

Clinical Characteristics: Three subgroups may be included in the description of porphyria [1f];

1. *Light sensitive porphyria* is rare and affects males more often than females. It is possibly inherited as a Mendelian recessive and usually appears early in life, accompanied by the excretion of large amounts of *uroporphyrin I,* which imparts a red or mahogany color to the urine. Coproporphyrin I may be present. Photosensitivity of the exposed areas of the skin with formation of bullae, scarring, contracture, and even loss of the digits is frequent.[1a] Reddish-brown pigmentation of the teeth and cartilages, splenomegaly and hirsutism are other features. Porphobilinogen is absent. Prognosis as to life is good, a protracted course being common.

2. *Acute intermittent porphyria* is inherited as a Mendelian dominant, appears later in life and affects females preponderantly. The first complaints may be referable to the abdomen, with simulation of an acute surgical condition, or the signs may point to the central nervous system. Fatal termination is not infrequent.[1a] Attacks occur intermittently, however, and the disease may endure for many years. Asymptomatic or latent forms may be discovered only by routine testing of the urine.

Alcohol, barbiturates and many chemotherapeutic agents have been indicted as precipitants of exacerbations of this disorder.[1c, 10b] Infection, exhaustion and anxiety have also been considered as additional factors.

The following manifestations are commonly encountered:

a. Nervousness, indigestion, and vague complaints referable to the gastrointestinal system.
b. Severe colicky abdominal pain and obstipation.
c. Skin pigmentation; photosensitivity is slight when present.
d. Weakness of the extremities, paresthesias, ascending paralysis and quadriplegia.
e. Convulsive seizures.
f. Hypertension.
g. Tachycardia and hoarseness.

The porphyrin excreted is mainly composed of uroporphyrin I in loose combination with a type III porphyrin.[28] Porphobilinogen is most frequently found

* The etioporphyrin isomers are labeled Types I, II, III and IV; the naturally occurring porphyrins, of known clinical significance, correspond to Types I and III.

in this type of porphyria; coproporphyrin III may also be present in varying amounts.

3. *Chronic porphyria* is actually a *"mixed"* form, presenting features of both the light sensitive and the acute types.   The term is misleading, for both so-called acute porphyria associated with acute episodes and light sensitive porphyria are chronic in nature.   Photosensitivity, abdominal complaints and absence of severe nervous symptoms are features of this form of porphyria.   The chemical findings vary considerably and are not characteristic.

Diagnosis: Examination of the urine for the colorless chromogen, porphobilinogen, and uroporphyrin provides the essential clue to the diagnosis of porphyria. Waldenström [2] considers porphobilinogen the colorless precursor of the two principal pigments of porphyria urine.   The Watson-Schwartz test for porphobilinogen is a simple screening test and, when positive, may be considered pathognomonic of the disease.[1d]   False-positive tests are extremely rare.[23]   Urine containing large amounts of porphyrins may be dark red in color; in some cases, however, freshly passed urine is light in color and darkens on standing for 24 hours, especially on exposure to sunlight.   Such specimens should be examined for the presence of porphyrins.   These substances may be further identified by specific absorption bands, solubilities, melting points, and other physicochemical properties.

On exposure to Wood's lamp, fluorescence of skin lesions may be demonstrable.   Urine containing porphyrins, when acidified, may also fluoresce.

Two properties of the porphyrins aid in explaining the presenting signs and symptomatology.   Photodynamic response, at least indirectly, is proposed as the basis for the skin lesions and the fluorescence of tissue and body fluids.   A spastic effect on smooth muscle accounts for the violent abdominal cramping, angiospasm and hypertension.   Surgeons exploring the abdominal contents of porphyric patients may observe viscera in spastic contraction.

Porphyrinuria: In general, the total urinary coproporphyrin is elevated in the presence of liver functional impairment.   This is usually due to the type I isomer, but if the injury is on the basis of chemical or metal toxicity it is more likely to be associated with an excessive type III excretion.[1f]

DISCUSSION

The index case (H) fulfilled the criteria for a diagnosis of porphyria.   The positive tests for porphobilinogen likewise confirmed the same diagnosis in F and G.   Although chemical confirmation of this diagnosis was lacking in the other members, history of their illnesses is compatible with the characteristics of porphyria.

Case H was studied with reference to adrenal insufficiency, but this diagnosis was excluded since normal findings were obtained with the Robinson-Kepler-Power water test, the glucose tolerance test, and the determination of total chlorides.   The notion that periodic dysfunction of the adrenals may occur on the basis of vasospasm with resultant ischemia cannot be dismissed.

The combination of abdominal symptoms and light-sensitivity, in the absence of severe nervous involvement, is a clinical rarity; the index case presented these features and closely resembles other reported cases of mixed porphyria.[5, 6, 11]

On clinical grounds, the other members of the family tend to conform to the description of the acute intermittent form of the disease.

In contrast to the usual sex distribution with female dominance, the male patients in this family outnumber the females six to two. This discrepancy may be more apparent than real, for the males manifest considerable gynic (feminine) emphasis in their androgynous patterns. The importance of extra-genital sex differences and the "mosaic of androgyny" has been emphasized by Draper [26] and is helpful in understanding the sex distribution of many diseases.

The clinical manifestations described in other reports on porphyria [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22] are well represented in this family (table 1). Hypertension was present in the first two generations (A, B, C), and neurologic involvement was prominent in the third generation (D, F, G, H). Cutaneous signs were present in varying degree with solar exposure as an apparent accessory factor. The index case had cutaneous fragility to such a degree that mild trauma produced lesions on the hands and arms, in this respect resembling epidermolysis bullosa, but differing in that sensitivity to both light and trauma was demonstrable.

The association between porphyria and jaundice, apparent in H, has been recognized by others.[1c, 7, 11, 19, 24] Positive cephalin flocculation tests indicated a hepatocellular origin of H's jaundice.

The occurrence of convulsive seizures among porphyric persons and the striking incidence observed in this family (D, F, G) suggest the inclusion of porphyria in the differential diagnosis of epileptic disorders. Porphyria also merits consideration in the differential evaluation of hypertension, "the surgical abdomen" and numerous clinical syndromes.

There is no specific treatment for these individuals. Avoidance of exposure to the sunlight and of fatigue, the cautious use of drugs, especially sulfonamides and barbiturates, an adequate diet, and interdiction of the use of alcohol are the chief prophylactic measures to be employed.

SUMMARY

1. A clinical triad of dark urine, visceral crises with obstipation, and photosensitivity of the skin led to the diagnosis of mixed porphyria in a 20 year old naval recruit.

2. Investigation of the family background yielded evidence of seven additional cases, as indicated by dark urine, visceral crises, bizarre behavior, convulsive seizures, hypertension and photosensitivity of the skin; these latter case histories tend to fit the description of acute intermittent porphyria.

3. Porphyria, known to some as "the simulator," may appear under many guises, frequently changing character, occasionally playing multiple rôles.

BIBLIOGRAPHY

1. a. Watson, C. J. in Cecil, R. L.: A textbook of medicine, ed. 7, 1947, W. B. Saunders & Co., Philadelphia, pp. 734-738.

27. Welcker, M. L.: The porphyrins, New England J. Med. **232**: 11–19, 1945.

28. Watson, C. J., Schwartz, S., and Hawkinson, V.: Studies of uroporphyrins. II. Further studies of porphyrins of urine, feces, bile, and liver in cases of porphyria, with particular reference to Waldenström type porphyrin behaving as entity on the Tswett column, J. Biol. Chem. **157**: 345–361, 1945.

PERICARDIECTOMY IN TWO CASES OF CHRONIC CONSTRICTIVE PERICARDITIS *

By Alexander E. W. Ada, M.D., Oswald R. Jones, M.D., F.A.C.P., and Archibald D. Sheeran, M.D., *New York, N. Y.*

THE purpose of this paper is to present the clinical syndrome of chronic constrictive pericarditis as it occurred in two patients on whom a total of three pericardial resections was done. Since Churchill[1] performed the first successful pericardial resection for chronic constrictive pericarditis in this country in 1928, a formidable literature, with particular emphasis on the surgical treatment of the disease, has developed in this country. There are several admirable discussions of the historic aspects of chronic constrictive pericarditis.[2, 3, 4, 5] The pioneer contributions of Churchill and White,[1, 2, 6] Blalock and Burwell,[3] and Beck[7] have been supplemented by the series of Neuhof, et al.,[8] Harrington,[9] and Heuer and Stewart.[4, 5] Sprague[10] discussed the differential diagnosis of congestive heart failure and chronic constrictive pericarditis. The pathologic changes characteristic of chronic constrictive pericarditis have been studied by Armstrong[11] and the well-defined differences between this condition and the pericardial changes produced by rheumatic fever carefully delineated. In 1941 Sodeman[12] correlated most of the information on the subject in an excellent review. The roentgenographic and roentgenoscopic signs of chronic constrictive pericarditis have been evaluated by Stewart, Carty and Seal.[13] Detailed studies of the altered circulatory dynamics in this disease were made by Lyons and Burwell.[14]

It is generally accepted that in chronic constrictive pericarditis there is a fibrous thickening of either the visceral or the parietal pericardium (or both), producing around the heart muscle a contracted scar which interferes mechanically with the diastolic filling of the heart chambers. Adhesions between the two layers may or may not be present. In some cases the pericardial sac is completely obliterated. White[6] found calcification present in 16 of 37 cases (43 per cent). Most investigators agree that the heart is either normal in size or slightly to moderately enlarged.

Tuberculosis is generally accepted as a valid etiologic factor. It was present in five of 37 cases in White's series,[6] in 18 of 28 in Blalock and Burwell's series,[3] in five of 24 cases in Harrington's series,[9] and in one of 18 cases in Heuer and Stewart's series.[5] A previous acute pericarditis, pneumonia or sepsis may be the underlying cause in a few cases, but in most the etiology is unknown. Almost all investigators agree that rheumatic fever does not cause chronic constrictive pericarditis.

Enlargement of the abdomen and exertional dyspnea are the most common symptoms. Orthopnea is usually absent. Leg edema and engorgement of the neck vessels are almost always present. Abdominal ascites, enlargement of the liver and distended neck veins are the most common physical findings. The systolic blood pressure is usually normal or low, with a decreased pulse pressure. Paradoxical pulse is usually present. The venous pressure is invariably elevated. Detailed studies of the circulation [14] reveal an increased A-V oxygen difference, prolonged circulation time, diminished cardiac output per minute, decreased stroke volume and a lower "cardiac index." Diurnal fluctuations in venous pressure have been found to correlate with variations in the blood volume rather than with changes in the cardiac output.[4]

The most reliable roentgenographic sign of chronic constrictive pericarditis is calcification. According to Stewart et al.,[13] this is best demonstrated in lateral roentgenograms, and occasionally heavy exposures are necessary to demonstrate its presence. They found that, in the absence of calcification, the most common roentgenographic signs are (a) a small and flattened or absent aortic knob; (b) an abnormal configuration of the cardiac silhouette (triangular or globular shape), and (c) evidence of pulmonary congestion. The most common roentgenoscopic signs [13] are (a) limitation of lateral shift with changes in position; (b) limitation of elongation of the heart with descent of the diaphragms; (c) decrease in amplitude of cardiac pulsations over portions or all of the cardiac silhouette, and (d) paradoxic motion or deformity of the diaphragm due to the tugging of adhesions. The roentgenkymogram may be of value in the study of cardiac pulsations.

The electrocardiogram is of great help in the diagnosis. It is abnormal in all cases,[6] with low voltage of the QRS waves, or abnormal T waves, or both. White [6] found auricular fibrillation in 14 of 37 cases (37 per cent). Heuer and Stewart [4] noted auricular fibrillation in five of 18 cases (28 per cent). Blalock and Burwell [3] noted this arrhythmia in four of 28 cases (14 per cent).

Postoperatively, no constant findings are noted either roentgenographically or electrocardiographically.

The operation employed is usually the Delorme procedure of pericardial resection, with certain individual variations. The amount of pericardium resected is largely determined by the pathologic conditions existing in each individual case. Frequently, when there are dense adhesions between the visceral and parietal pericardium, an adequate cleavage plane cannot be found. Harrington [2] feels that as much as possible of the pericardium should be freed from the ventricles, the right auricle and the orifice of the inferior vena cava. He also believes that the attachments of the right ventricle to the diaphragm should be separated and the apex freed. Then he resects as much of the anterior portion of the pericardium as possible without injuring the pleura.

In 1946 Heuer and Stewart [5] assembled from the literature 256 patients who underwent pericardiectomy and found a primary mortality of 29 per cent. It is reasonable to assume that, with earlier recognition of the syndrome produced by chronic constrictive pericarditis, improved anesthesia technics, more complete knowledge of the physiology of the heart and circulation, and careful preoperative and postoperative care, this figure can be appreciably lowered.

The two patients whose records follow were successfully treated by pericardiectomy.

CASE REPORTS

Case 1. A 35 year old married communications worker was first admitted to
St. Luke's Hospital on August 27, 1942, complaining of swelling of the legs and
abdomen. In addition to the usual contagious diseases, he had contracted both scarlet
fever and diphtheria as a child. Other than these contagious illnesses, which left
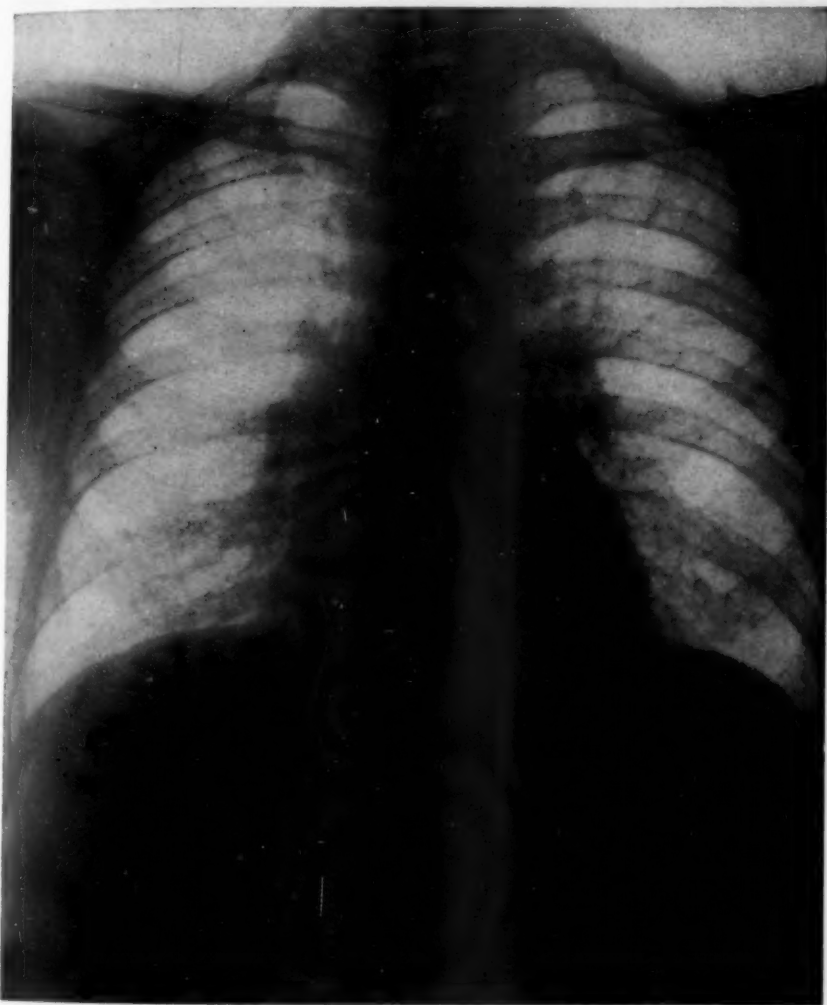
FIG. 1. *Case 1.* Antero-posterior view of chest showing moderate pulmonary congestion;
no calcification visible.

no known sequelae, he enjoyed excellent health until one year before admission when,
after one week's bout of fever and night sweats, he was told that he had "pericarditis."
Roentgenograms and an electrocardiogram, in addition to other studies, were done
by his physician at this time to support the diagnosis. He was sent to a sanatorium
for bed rest and, after a four to five week period, was slowly mobilized and soon

resumed his work. Following this episode he complained of transitory exertional dyspnea, which soon disappeared. He was well until 12 to 16 weeks before admission, when he noticed an increasing abdominal girth, and 10 weeks before admission he first noted that his ankles were swollen. Swelling of the abdomen and ankles increased progressively. At no time did he experience chills or fever.

Review of the systems was essentially negative. There was no familial history of tuberculosis.
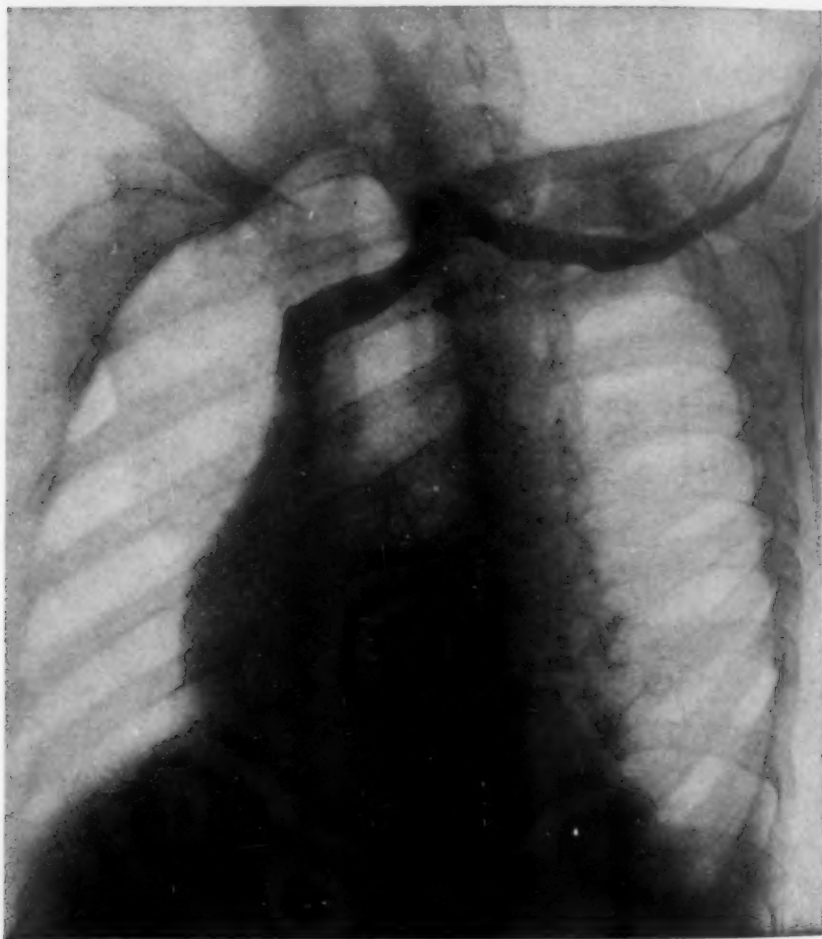
Fig. 2. *Case 1.* Angiocardiogram illustrating normal innominate and superior vena cava.

Physical examination on admission revealed the following findings: The temperature was normal; respirations, 20; pulse, 100; blood pressure, 103 mm. Hg systolic and 78 mm. diastolic. Although the neck veins were distended, the patient was comfortable flat in bed. The chest was moderately emphysematous, with dullness and diminished breath sounds at both bases. No râles were heard. The heart was moderately enlarged to percussion. The heart sounds were regular and distant, with no audible murmurs. Pulsus paradoxus was present. Abdominal examination re-

vealed a moderate ascites, with all confirmatory signs present. The liver, smooth and nontender, extended 6 cm. below the costal margin. There was a 3 plus pitting edema of the ankles and legs to the midcalf.

Admission laboratory data were as follows: Urinalysis: negative; hemoglobin: 13.7 gm.; red blood cells: 4.5 million; white blood cells: 5,400, with 74 per cent polymorphonuclears, 22 per cent lymphocytes and 4 per cent monocytes. Kline test: negative. Urea nitrogen: 11.4 mg. per cent. Total serum proteins: 7.25 gm. Sedimentation rate: 3 mm./hr. Cephalin-cholesterol flocculation test: 4 plus. Phenolsulfonephthalein showed 73 per cent total excretion at two hours.

Fig. 3. *Case 1.* Antero-posterior view of chest four years after pericardiectomy and spine fusion.

Course: In view of the history and physical findings, pericardial disease was suspected, and the initial roentgen-ray studies were corroborative. The roentgenologist reported a moderate generalized cardiac enlargement, with the lung fields essentially clear except for a moderate circulatory congestion. There was no evidence of pleural exudate, but some pleural adhesions were present in the left lower lobe posterior to the heart. At fluoroscopy there was marked restriction in the amplitude of contractions, particularly of the left ventricle. Moderate enlargement of the right auricle and slight enlargement of the right ventricle were demonstrated. There was no evidence of calcification. The routine admission electrocardiogram disclosed the existence of low R waves and isoelectric T waves in all leads, with a moderate left axis deviation. Five days later, in a second electrocardiogram, low voltage in

all leads was again demonstrated. These findings also were consistent with constrictive pericardial disease.

The venous pressure showed moderate elevation (200 mm. saline), and the circulation times were similarly impaired (arm to lung, using ether, was 12 seconds; and arm to tongue, using calcium gluconate, was 45 seconds).

With no treatment other than bed rest, the patient lost 26.75 pounds in the first

FIG. 4. *Case 2.* Antero-posterior view of chest showing ring shadow due to calcified pericardium.

10 days. Although the edema and ascites disappeared, the liver remained enlarged. When improvement appeared to be static, pericardiectomy was advised.

On September 17, 1942, under endotracheal anesthesia, a curved incision was made over the left anterior chest wall, the skin and muscles were reflected laterally, and the third, fourth, fifth and sixth left ribs, along with their costal cartilages, were resected from the anterior axillary line to the border of the sternum. The parietal pericardium was found to be markedly thickened and fairly firmly adherent to the visceral pericardium. After lysis of all adhesions, the parietal pericardium over-

lying the ventricle anteriorly was resected, allowing a noticeable increase in the diastolic filling of the heart.

The postoperative course was uneventful except for the accumulation of fluid in the left chest, which was treated by thoracenteses. Blood-tinged fluid was removed on three occasions but tended to reaccumulate. The venous pressure on September 19, 1942, two days after the operation, was 134 mm. saline. Subsequent determinations of the venous pressure were:

> September 23, 1942—145 mm. saline
> September 25, 1942—155 mm. saline
> September 30, 1942—210 mm. saline
> October   22, 1942—170 mm. saline

The electrocardiogram following operation showed evidence of slight improvement in that there was an increase in the amplitude of the major deflections; however, the T wave changes persisted. The pleural exudate in the left chest was the major postoperative problem and was checked with serial roentgenograms. When the process appeared stabilized, the patient was discharged to the Convalescent Hospital.

Microscopic examination of the tissue removed at operation showed that the pericardium was very thick and composed of dense fibrous tissue, with slight perivascular infiltration around the blood vessels. The cells were chiefly lymphocytes, with occasional eosinophils. There were fresh hemorrhages into the tissue on the internal aspect, but no other cellular infiltration. There were no tubercles or other direct evidence as to etiology. The pathologic diagnosis was "chronic pericarditis."

After one week at the Convalescent Hospital, despite limited activity, ankle edema reappeared and the fluid in the left chest increased slightly. The patient was readmitted to the hospital from November 4, 1942, to January 9, 1943, and a total of six left thoracenteses was done. In addition, on December 2, 1942, 30 c.c. of 70 per cent Diodrast were injected into an arm vein, but evidence of adhesions or of any other form of obstruction around the superior vena cava was not demonstrated. The venous pressure on this admission was 186 mm. saline, and the circulation times were: arm to tongue, using calcium gluconate, 25 seconds; arm to lung, using paraldehyde, 21 seconds. No definite treatment program was initiated, although mercurial diuretics consistently reduced the ankle edema. The patient was then discharged to the Surgical Clinic, where treatment with ammonium chloride and bi-weekly injections of mercuzanthin was continued. He slowly but progressively improved, and returned to work in February, 1943. In March, 1944, because of an increase in ankle edema and slight dyspnea, he was again readmitted for thoracentesis, and 1,000 c.c. of clear yellow fluid were removed. At this time the blood pressure was 120 mm. Hg systolic and 90 mm. diastolic. Other than the signs of left hydrothorax, a heart which was slightly enlarged to the left, and a liver which extended 4 cm. below the costal margin, there were no significant physical findings.

Again in July, 1944, the patient was readmitted, this time complaining of a poorly localized midline pain in the anterior chest of two weeks' duration. The pain radiated through to the back and was aggravated by change in position. The physical examination was essentially unchanged. After 1,200 c.c. of clear yellow fluid had been withdrawn from the left chest, a roentgenogram, in addition to demonstrating a pleural exudate which obscured the lower one-third of the left chest, revealed a fusiform widening of the inferior mediastinum. A lateral film showed that this was secondary to tuberculous spondylitis involving the sixth and seventh thoracic vertebrae, with marked collapse of the sixth vertebral body, destruction of the intervertebral disk, and a localized kyphosis of the spine. There was no evidence of tuberculous infiltration in the lung fields. Spot films of the involved area confirmed the diagnosis of tuberculous arthritis complicated by a paraspinal abscess. Guinea pig inoculation of the chest fluid yielded negative results. The patient was transferred

to the Orthopedic Service, where several spinal fusions were done, and after a period of sanatorium care he returned to work (January, 1946) free of cardiac and spinal symptoms. His subsequent follow-up examinations in the Surgical Clinic revealed that the patient was asymptomatic.

Case 2. The second patient, a single Irish blacksmith's helper, 43 years of age, was first admitted to St. Luke's Hospital on August 6, 1945. He complained of swelling of the ankles and abdomen. He had been in good health until nine months before admission, when he noticed the insidious onset of these symptoms, which were not accompanied by dyspnea, orthopnea or chest pain. At that time he had been
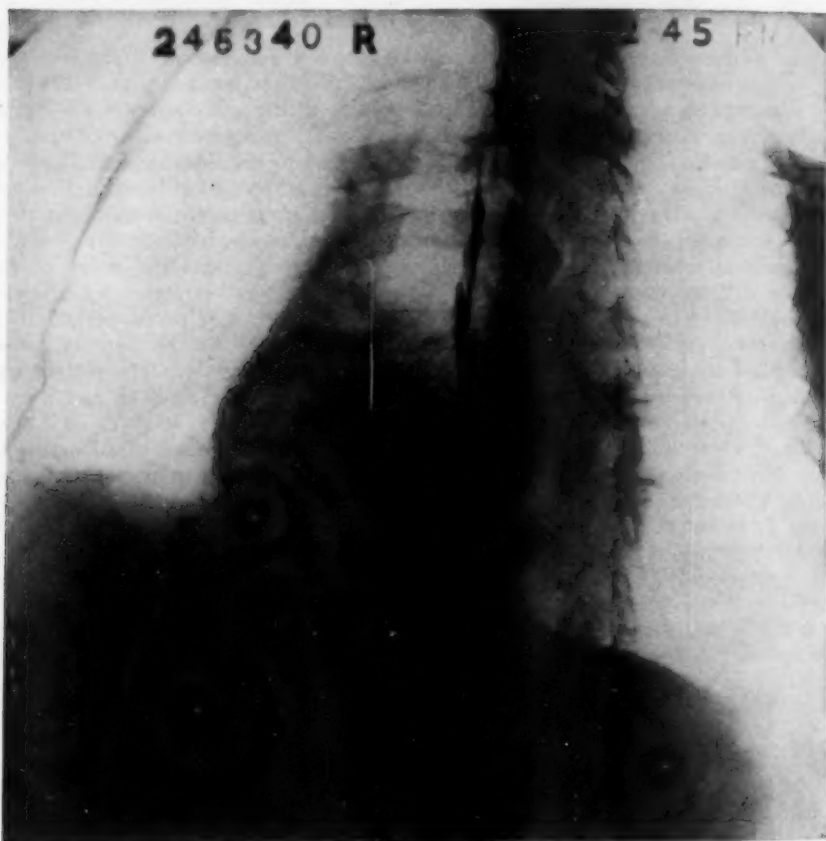
FIG. 5. *Case 2.* Lateral view of chest showing calcification of pericardium.

admitted to a local hospital and given digitalis and diuretics, which almost completely relieved the swelling. After discharge he had taken his medications sporadically, but six months later had again entered the same local hospital because of a recurrence of the swelling. On the second occasion, after digitalis and diuretics failed, an abdominal paracentesis had been done. This procedure gave great relief, and he did well until three weeks before admission to St. Luke's Hospital, when the swelling reappeared. There was no history of tuberculosis or rheumatic fever. Although he admitted that his alcoholic consumption had been considerable for 20 years, he was never jaundiced; no history of hematemesis or melena was given.

On physical examination it was found that the heart was moderately enlarged to the left. The rhythm was irregular, with a rate of 100 beats to the minute. No murmurs were heard. The blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. There were scattered wheezes in both lungs. He had a massive abdominal ascites, with 4 plus edema of the legs and ankles.

Laboratory data were as follows: Urinalysis: negative; hemoglobin: 13.0 gm.; red blood cells: 4.6 million; white blood cells: 6,700, with 62 per cent polymorphonuclears, 30 per cent lymphocytes, 4 per cent monocytes, and 4 per cent eosinophils. Mazzini: negative. Urea nitrogen: 13.4 mg. per cent. Total serum proteins: 6.9

FIG. 6. *Case 2.* Antero-posterior view of chest two years after pericardiectomy (bilateral approach).

gm. (albumin 4.3, globulin 2.6). Cephalin-cholesterol flocculation test: 2 plus. Sedimentation rate: 16 mm./hr. Repeated stool examinations for occult blood were negative.

The initial roentgenogram of the chest revealed a moderate, generalized hypertrophy of the heart and considerable uniform dilatation of the aorta. There was a considerable degree of circulatory congestion throughout both lungs, complicated by pleural exudate in the costophrenic sulci, with a trace in the interlobar fissures. Serial electrocardiograms revealed auricular fibrillation as a constant finding. He was given a high protein, high caloric diet, with massive doses of vitamins; in addi-

tion, he was digitalized. Mercuzanthin and ammonium chloride were used as diuretics. Two abdominal paracenteses were done, the ascitic fluid showing the characteristics of a transudate. After 31 days in the hospital, he showed great improvement and was sent to the Convalescent Hospital, but returned nine days later because of rapid reaccumulation of the ascitic and edema fluid. Two more abdominal paracenteses were done, and after approximately two hospitalization weeks he was discharged to the clinic.

Again, in two weeks' time (October 15, 1945), he was referred for readmission

FIG. 7. *Case 2.* Constrictive pericarditis scars showing bilateral approach to pericardium.

because of the same complaints. While he was being fluoroscoped for esophageal studies it was noted that the anterior half of the heart was covered by confluent areas of dense calcification in the pericardium extending to the base of the aorta, over the pulmonary conus, the surface of both the right and left ventricles, and the diaphragmatic aspect of the pericardium. The auricular portion of the heart did not show any pericardial calcification. At fluoroscopy there was marked restriction of motion in the calcified areas. There was considerable hypertrophy of both the right and left auricles, producing slight backward displacement of the barium-filled esophagus. His venous pressure in October, 1945, was 253 mm. saline; it remained

consistently elevated in subsequent determinations. Although various cardiac murmurs were described on several occasions, the cardiostethogram revealed no significant murmurs. Laboratory studies indicated a moderate impairment of liver function. Peritoneoscopy on October 15, 1945, revealed a moderately enlarged and nodular liver with a granular surface. It was firm in consistency and so fibrous in nature that attempted biopsy was unsuccessful. The liver was reported to have the typical gross appearance of Laennec's cirrhosis.

It was fairly well established that the ascites, with both Laennec's cirrhosis and constrictive pericarditis as etiologic factors, was not amenable to the more conservative forms of treatment. Since repeated paracenteses gave only temporary relief, pericardiectomy, with removal of one of the causes, was elected as the procedure most likely to produce the greatest improvement.

On February 6, 1946, using a left-sided approach, a subtotal pericardiectomy was performed. The posterior 40 per cent of the parietal pericardium was adherent to the visceral pericardium, covering the right ventricle, right auricle and inferior vena cava. This portion showed a considerable degree of calcification. The anterior 60 per cent of the parietal pericardium was thickened but not adherent or grossly calcified. Two large portions of visceral pericardium were carefully dissected and excised from the anterior and lateral aspects of the heart. It was estimated that the resected portions comprised 60 per cent of the entire pericardium. Release of the constrictions about the inferior vena cava was impossible because of inadequate exposure and dense adhesions. The pathologist's report was "chronic pericarditis, calcified."

The postoperative course was uneventful. A venous pressure, done six days after operation, was 130 mm. of saline, substantially lower than the preoperative level. This improvement proved to be a temporary phenomenon, however, since 20 days after operation the venous pressure returned to a high level (300 mm. of saline), where it remained (185 to 300 mm. of saline) on serial determinations done in the following months.

It was soon found that, although the amount of pericardium removed was more than adequate for the average case of constrictive pericarditis, the patient failed to show any improvement. An abdominal paracentesis was required every two weeks. Operative intervention, using a right-sided approach, was finally deemed advisable, and on October 30, 1946, a right thoracotomy was done and the calcified portion of pericardium overlying the right lateral aspect of the right ventricle and the adjacent portion of the inferior vena cava was removed. In attempting to remove the closely adherent calcified pericardium over the right auricle, the auricle was inadvertently entered and a massive hemorrhage ensued. The bleeding from the 1.5 cm. aperture in the right auricle was controlled by digital pressure and an autotransfusion was arranged, the patient receiving approximately 1,200 c.c. of his own blood while the defect in the right auricle was closed by a series of interrupted sutures of No. 1 silk. No further pericardial surgery was attempted, and the wound was closed in layers. In addition to the autotransfusion, 1,500 c.c. of blood bank blood were given during the operation.

Recovery was uneventful. The venous pressure fluctuated widely after operation, reaching its lowest value two months postoperatively (154 mm. of saline). With digitoxin and frequent injections of mercuhydrin, ambulatory status for the first time became practical. No further abdominal paracenteses were necessary after the second operation. Gradual improvement continued, finally reaching the point where he was considered employable. A job as elevator operator was obtained for him, and he was discharged from the hospital on July 10, 1947. Under clinic care he continued to do well until October, 1947, when he was admitted for abdominal para-

centesis; 6,000 c.c. were obtained. At this time his venous pressure was 170 mm. of saline. From February 24, 1948, to March 17, 1948, he was again hospitalized with an arterial embolism involving a branch of the left popliteal artery. For this he received heparin and Dicumarol. After an uneventful recovery he was discharged on a maintenance ration of Dicumarol, the dosage of which was determined by weekly tests of the prothrombin activity. He has remained on this drug until the present. During the period from March, 1948, until the present time he has made remarkable progress, and now requires mercurial injections only at intervals of from two to four weeks.

COMMENT

Both cases exhibited most of the classic symptoms and signs of chronic constrictive pericarditis. Both had ascites with hepatic enlargement, leg edema, elevated venous pressure, prolonged circulation times and slightly lowered blood pressure. Neither complained of orthopnea, and only in the first case was there exertional dyspnea. Both had moderate cardiac enlargement, and in the second case there were both pericardial calcification and auricular fibrillation. The electrocardiogram in the first case was typical of the usual tracings found in chronic constrictive pericarditis. Both had diminished pulsations on roentgenoscopic examination.

The etiology of the pericarditis in the second case remains obscure. With a history strongly suggestive of chronic malnutrition accompanying chronic alcoholism, and the peritoneoscopic findings of a nodular liver, it is probable that he also had Laennec's cirrhosis. Impaired liver function, of course, would occur with either disease. In the first case, positive evidence of tuberculosis was lacking as far as the microscopic study of the pericardial tissue was concerned. In addition, guinea pig inoculation of the chest fluid yielded negative results. However, in retrospect, with the development of a typical tuberculous spondylitis shortly after the initial pericardial disease, it is probable that tuberculosis was the etiologic factor responsible for the development of the chronic constrictive pericarditis. At no time were tuberculous lesions found in the lung parenchyma. Whether the original pericarditis represented the so-called "primary tuberculous pericarditis" (as described and reviewed recently by Stepman and Owyang[15]) is problematic.

In the second case, the primary pericardial resection using the conventional left-sided approach resulted in no improvement, although an estimated 60 per cent of the pericardium was removed. It was not until a secondary operation using a right-sided approach was performed that improvement began. Neuhof et al.[8] report using a two-stage procedure for effective decortication in three cases. In one of 18 cases reported by Heuer and Stewart,[4] a right-sided approach for secondary pericardiectomy was done. Similarly, White[6] had one case in which further pericardial resection was performed two years after the primary operation.

The first case was working full time 31 months after operation and had no complaints referable to his heart. There were no signs of cardiac decompensation, and his tuberculous process was apparently arrested. The second case was much improved two years after his operation, although he was forced to limit

his activity somewhat.   To control his leg edema a maintenance ration of mercu-
hydrin was necessary.

The prognosis and period of recovery depend on the duration of the disease,
age of patient and, most important, the extent of myocardial impairment.   In
some cases the response is dramatic and there is a rapid return to normal, while
other cases may require nine months to a year.

SUMMARY

1. Two cases of chronic constrictive pericarditis are presented.   Three peri-
cardial resections were done.

2. In each case a marked improvement as a result of the operative procedure
was noted.

3. The clinical syndrome of chronic constrictive pericarditis is reviewed
briefly.

BIBLIOGRAPHY

1. Churchill, E. W.: Decortication of the heart (Delorme) for adhesive pericarditis, Arch.
   Surg. 19: 1457, 1929.

2. White, P. D.: Chronic constrictive pericarditis treated by pericardial resection, Lancet
   2: 539, 597, 1935.

3. Blalock, A., and Burwell, C. S.: Chronic pericardial disease: report of 28 cases of con-
   strictive pericarditis, Surg., Gynec. and Obst. 73: 433, 1941.

4. Heuer, G. J., and Stewart, H. J.: The surgical treatment of chronic constrictive peri-
   carditis, New York State J. Med. 45: 993, 1945.

5. Heuer, G. J., and Stewart, H. J.: The surgical treatment of chronic constrictive peri-
   carditis, S. Clin. North America 26: 477, 1946.

6. Harrison, M. B., and White, P. D.: Chronic constrictive pericarditis—a follow-up study
   of 37 cases, Ann. Int. Med. 17: 790, 1942.

7. Beck, C. S., and Cushing, E. H.: Circulatory stasis of intrapericardial origin, J. A. M. A.
   102: 1543, 1934.

8. Oppenheimer, B. S., Hitzig, W. M., and Neuhof, H.: Chronic constrictive pericarditis:
   medical and surgical aspects, J. Mt. Sinai Hosp. 7: 270, 1941.

9. Harrington, S. W.: Chronic constrictive pericarditis: partial pericardiectomy and epi-
   cardiolysis in 24 cases, Ann. Surg. 120: 468, 1944.

10. Sprague, H. B.: The differential diagnosis of congestive heart failure and constrictive
    pericarditis, Am. Heart J. 12: 443, 1936.

11. Armstrong, T. G.: Adherent pericardium—constrictive and non-constrictive, Lancet 2:
    475, 1940.

12. Sodeman, W. A.: Chronic constrictive pericarditis, Am. J. M. Sc. 202: 127, 1941.

13. Stewart, H. J., Carty, J. R., and Seal, J. R.: Contributions of roentgenology to the
    diagnosis of chronic constrictive pericarditis, Am. J. Roentgenol. 49: 349, 1943.

14. Lyons, R. H., and Burwell, C. S.: Induced changes in circulation in constrictive peri-
    carditis, Brit. Heart J. 8: 33, 1946.

15. Stepman, T. R., and Owyang, E.: Clinically primary tuberculous pericarditis, Ann.
    Int. Med. 27: 914, 1947.

DISSEMINATED CALCIFICATION OF THE PANCREAS: REPORT OF TWO CASES *

By John H. Kneidel, M.D., *Indianapolis, Indiana*

Reports of disseminated calcification of the pancreas are becoming more frequent since the suggestion by Beling [1] in 1940 that it be distinguished from the more common type of pancreatic lithiasis. Beling found 12 cases from the literature prior to 1940 and added one of his own; Present and Geyman [2] added a case in 1947 and claimed that 19 cases were thereby on record. An excellent review by Wirts and Snape [3] shows a total of 24 cases, including the two which they reported. Epstein and Isaacs [4] reported an additional case in 1948, and Reeves and Moran [5] added six more cases, bringing the total to 31. This relatively small number of cases of disseminated pancreatic calcification is in sharp contrast to the 220 cases of pancreatic calculi accumulated from the literature by Jaleski [6] prior to 1942.

Pancreatic calcification is predominantly a disease of middle-aged males. It is significant that there is no characteristic clinical syndrome. The most constant feature is a variable type of epigastric pain which is usually dull and continual in character, with periods of acute colicky exacerbations. Lumbar radiation of the pain is common, and the acute attack is most often confused with gall bladder or renal disease. A high incidence of alcoholism with pancreatic calcification has been noted. Steatorrhea with severe diarrhea of bulky fatty stools develops in the well established case; this apparently results from a lack of secretion of the pancreatic fat-splitting hormone steapsin. Diabetes is a late and terminal manifestation resulting from destruction of the islands of Langerhans through parenchymal atrophy and fibrosis.

The pathology of pancreatic calcification has special historic interest. Opie [7] indicated in 1900 that obstruction of the pancreatic ducts was followed by a parenchymal atrophy of the pancreas, but that diabetes did not develop so long as the islands of Langerhans remained intact. Reputedly, it was Barron's [8] report of a case of pancreatic lithiasis associated with diabetes that first stimulated Banting to his discovery of the hormone insulin. The cause of pancreatic calcification in general remains obscure, but it is generally assumed that it is a combination of stasis of secretion in the ducts with bouts of pancreatitis. Seegar [9] pointed out that the pancreas does not normally secrete calcium, but that pancreatic calculi are composed for the most part of calcium carbonate. This suggested that some underlying pancreatic disturbance must be present for calcification to occur. The answer seems to have been supplied by Edmondson and Fields, [10] who found that there is a marked tendency for the pancreas to mobilize calcium in acute pancreatitis. Rienhoff and Lewis [11] have shown that pancreatic calculi can precipitate bouts of acute pancreatitis. It seems reasonable, then, to assume that the basis for disseminated calcification of the pancreas is a combination of factors working in a somewhat vicious cycle. Duct calculi could produce bouts of acute pancreatitis with focal areas of parenchymal necrosis which later

calcify. Some of this latter calcification could be discharged into the duct system, resulting in further difficulty. Surgical removal of pancreatic duct calculi would seem indicated whenever possible.

In those cases of disseminated pancreatic calcification observed at autopsy a fairly characteristic pathologic picture is seen. There is calcification in both the larger and the smaller ducts, with cystic dilatation of these ducts. Foci of calcification may also be seen in the remaining parenchymal tissue. A chronic interlobular pancreatitis, which in the later stages progresses to a marked interstitial fibrosis, is seen. There is atrophy of the parenchymal acinar tissue, with a severe degree of fibrosis. Diabetes is a late sequela, since the islands of Langerhans are the last structures to be destroyed.

At present the diagnosis of pancreatic calcification depends for the most part on the radiologic findings correlated with the clinical picture. Gillies [12] found that the calcifications were, for the most part, located somewhere below a horizontal plane passing through the upper margins of the body of the first lumbar and above a plane through the lower margin of the third lumbar vertebrae. The calcifications may be found above this level but never below it. Because barium
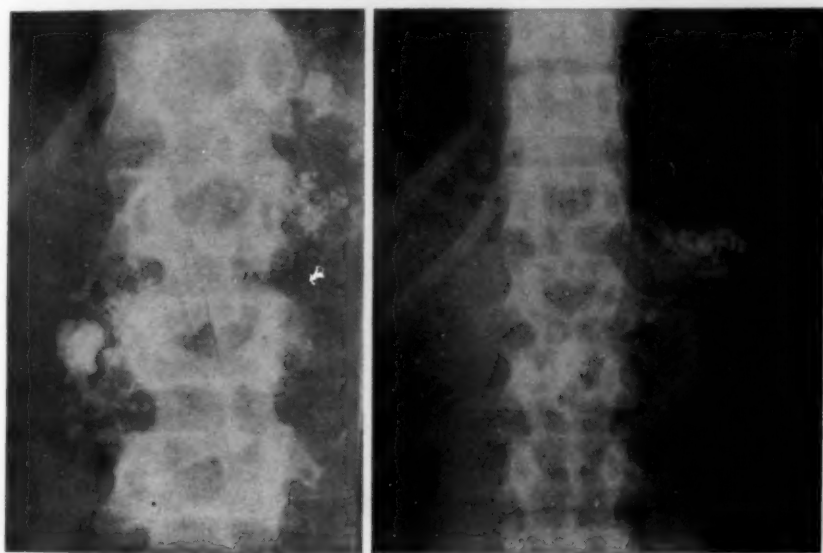
Fig. 1. Radiographs of the upper abdomen of case 1 clearly demonstrate the calcifications disseminated throughout the area of the pancreas.

in the stomach or colon can obscure the calcifications, scout films in the AP and lateral projections are essential. The lateral view is important, since the pancreas is a retroperitoneal organ and usually lies 1 to 2 cm. in front of the spine. The tail, however, may curve posteriorly to be situated in the same plane as the vertebral bodies. Another diagnostic roentgen aid is the demonstration of certain alterations in small bowel normal function, which are believed to result from associated pancreatic insufficiency. Such a case was well described by Sage [13] in 1945. Laboratory studies to demonstrate pancreatic insufficiency are success-

ful only in the late stages of the disease, and they certainly occupy a secondary place to radiographic methods of diagnosis of the condition.

Following is a report of two cases of disseminated pancreatic calcification associated with diabetes. One case was followed to autopsy.

CASE REPORTS

Case 1. A 33 year old white male was admitted to Indianapolis General Hospital with the complaints of severe cramping epigastric pain, voracious appetite, diarrhea with profuse, foul-smelling stools, weakness and weight loss. Attacks of abdominal colic had occurred since the age of eight years. These came about twice a year and were accompanied by jaundice. Following each attack of colic a fatty diarrhea would develop which lasted for two to three days. Four years prior to the

FIG. 2. A radiograph of the upper abdomen of case 2 reveals calcifications measuring 0.2 to 1.5 cm. in average diameter throughout the pancreatic area.

present admission diabetes mellitus had been diagnosed. A weight loss of 50 pounds had occurred over a period of four years, the patient going from 160 to 110 pounds.

The family history revealed that a sister and a cousin of the patient were diabetics.

The physical examination revealed a lethargic, poorly nourished and extremely emaciated white male. There was a chronic draining ulcer on the right thigh. Abdominal tenderness was elicited, with localization about 2 inches to the right of the umbilicus.

Radiographic examination of the abdomen was made (figure 1), and the diagnosis of disseminated pancreatic calcification was established.

General opinion was that the patient had diabetes of average severity. Fasting blood sugars with no insulin were 200 mg. to 250 mg., while on 20 units of protamine and 5 units of regular insulin the fasting blood sugars were found to stay around 80 to 100 mg. per cent. Control of the diabetes was greatly hindered by the persistent diarrhea. It was found that during bouts of diarrhea the blood sugar fell rapidly and the patient almost always went into insulin shock. Fatty foods were shown to

cause exacerbations of the diarrhea. The diarrhea was believed to be caused by the pancreatic insufficiency.

The patient was discharged from the hospital but was readmitted during the following months because of insulin reactions. The final admission was in December of 1942. He had continued to lose weight and strength until he now weighed only 85 pounds. A chronic productive cough with blood-streaked sputum had developed. A film of the chest revealed far-advanced pulmonary tuberculosis. During this final hospital stay frequent insulin reactions occurred. The patient died on January 11, 1943, followed a period of hypoglycemia. No autopsy was performed.

Case 2. A 45 year old Negro woman was seen as an outpatient in Indianapolis General Hospital in October, 1946, complaining of abdominal pain and distention,
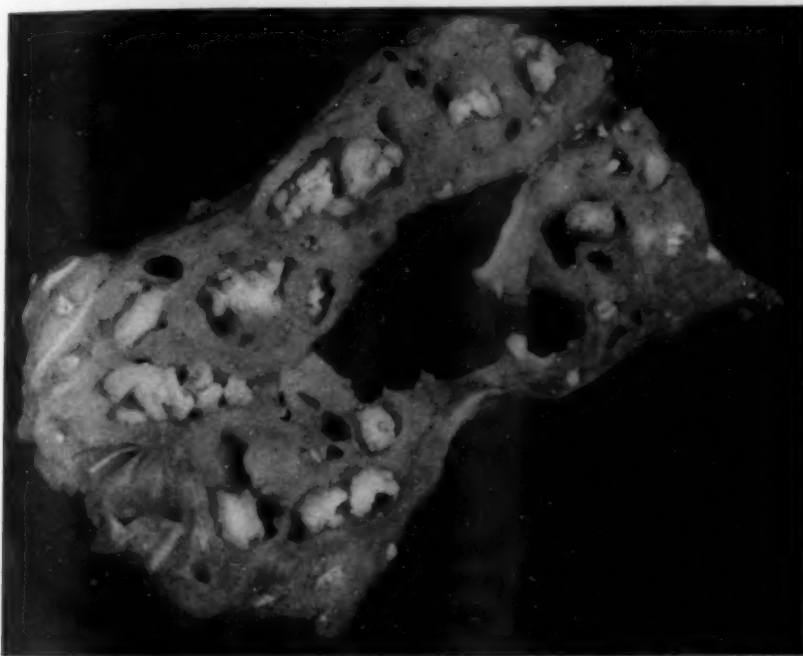
Fig. 3. Gross study of the cut section of the pancreas from case 2 shows calcium carbonate calculi throughout the duct system. The ducts are dilated, fibrous and cystic. Marked fibrosis of the entire pancreas is evident.

weakness and increased appetite. These symptoms had been present for about a year and a half, with the patient gradually becoming more debilitated. A weight loss of 45 pounds had occurred over a period of one year.

Physical examination revealed an emaciated Negro woman who appeared older than her stated age. The abdomen was pendulous, with a large, well-defined firm mass extending upward from the right lower quadrant. It was decided that this was most likely a large ovarian cyst. Urine analysis showed a 4 plus sugar reaction, and blood sugar estimations indicated a rather severe degree of diabetes to be present. The blood sugar levels were 450 to 500 mg. per cent fasting, while postprandially, following doses of 20 units of protamine zinc and 40 units of regular insulin daily, the blood sugar ranged from 250 to 334 mg. per cent. There was constant glycosuria

and no tendency toward insulin reactions during this admission. Radiographic examination of the abdomen revealed extensive calcifications throughout the region of the pancreas (figure 2). There were, however, no remarkable epigastric pain and no diarrhea.

This patient left the hospital against advice and did not return until six months later. At this time she was admitted with severe diarrhea and convulsions which had occurred for several days. No insulin had been taken at home. Although noisy and disoriented she did not appear to be in diabetic coma. Blood sugar was
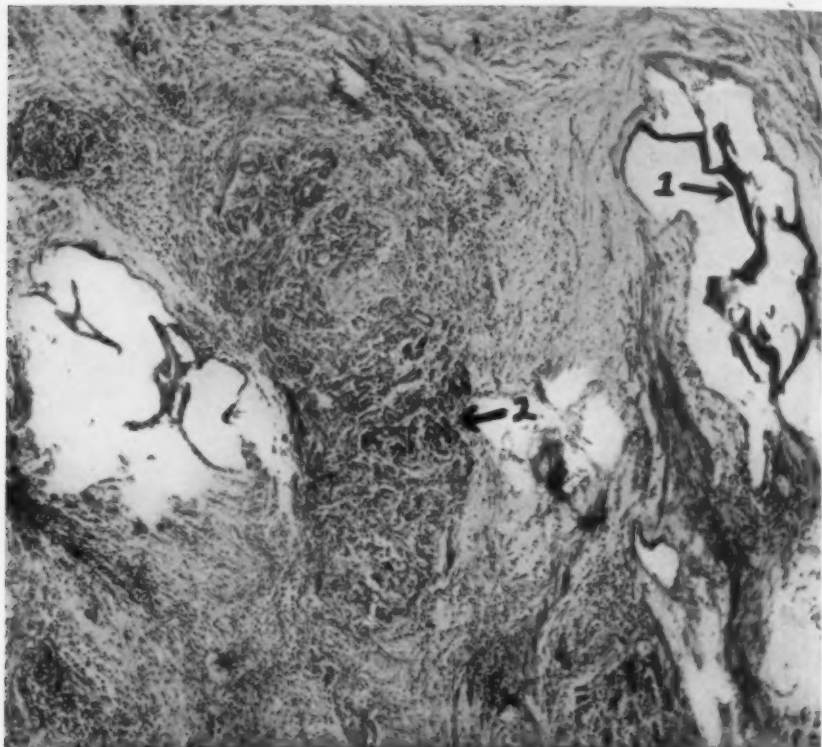
FIG. 4. A photomicrograph of case 2 (high power) shows calcification within a small duct (1). A small focus of remaining glandular cells is seen (2). Interlobular fibrosis and focal areas of small round cell infiltration form prominent features of the microscopic study.

431 mg. per cent. The patient was given 25 units of insulin on admission and 40 units of protamine zinc and 20 units of regular insulin before breakfast the following morning; however, she could not eat. She died five days after admission without regaining complete consciousness.

The significant findings of the postmortem examination were limited to the abdomen. There was a large (15 cm. in diameter) simple serous cyst of the right ovary. This obstructed the right ureter through extrinsic pressure, and had caused a hydronephrosis (grade 2) of the right kidney. The colon was filled with bulky, foul-smelling, yellow, greasy fatty material. A peculiar crepitus was elicited on palpation of the pancreas. This organ seemed fibrotic and filled with gritty stony

material. Gross study of the pancreas (figure 3) showed the large and small pancreatic ducts to be filled with calculi. The pancreatic ducts were dilated and in areas appeared mildly cystic. Microscopic study of the pancreas (figure 4) showed a fibrosis of the gland with dilatation of the ducts. Only a minor amount of parenchymal acinar tissue remained. There were scattered areas of small round cell infiltration, most marked in the interlobular interstitial tissue. The ducts showed fibrous thickening of their walls. The islands of Langerhans were still discernible. Calcifications could be identified throughout the duct system.

COMMENT

It seems noteworthy that, in case 1 and possibly in case 2, insulin shock was precipitated by exacerbations of diarrhea. This was apparently the result of an increased loss of carbohydrate in the stools and poor intestinal food absorption due to the pancreatic steatorrhea. Thus it would seem that diabetes associated with disseminated pancreatic calcification constitutes a special problem so far as its control is concerned.

The long history of abdominal colic in case 1, dating back to the age of eight years in this 33 year old male, suggests that the pancreatic disease had been present for some time prior to its discovery. Similar instances pointing to a long chronicity of the process are on record and indicate the likelihood of recurring bouts of pancreatitis. The attacks of jaundice which this patient experienced, associated with abdominal colic and diarrhea, are of interest since pancreatic duct calculi can cause obstruction of the bile duct as they become arrested at the ampulla of Vater.

It behooves the internist and the radiologist to consider pancreatic disease when gastrointestinal, gall bladder and kidney studies have not determined the cause for abdominal symptoms. The diagnosis of pancreatic calcification can usually be made directly from the plain film, although calcified retroperitoneal nodes and splenic vessel calcifications may be sources of error. The importance of the correct diagnosis of the condition lies in giving proper management and prognosis to these cases.

SUMMARY

1. Two cases of disseminated pancreatic calcification complicated by diabetes and severe pancreatic insufficiency with steatorrhea are reported.

2. The diagnosis of pancreatic lithiasis depends on roentgen methods utilizing both scout films of the abdomen and small bowel study to determine alterations in the function of the small bowel.

3. Insulin therapy produced hypoglycemia in both of these diabetic patients because of an inability to maintain the food intake due to bouts of uncontrollable diarrhea.

4. The calcifications in case 2 were found to lie throughout the duct system of the pancreas.

BIBLIOGRAPHY

1. Beling, C. A.: Calcification of the pancreas, Am. J. Digest. Dis. 7: 231–234, 1940.
2. Present, A. J., and Geyman, M. J.: Diffuse calcification of the pancreas, Radiology 48: 29–32, 1947.

3. Wirts, C. W., Jr., and Snape, W. J.: Disseminated calcification of the pancreas: sub-
    acute and chronic pancreatitis, Am. J. M. Sc. 213: 290–299, 1947.
4. Epstein, B. S., and Isaacs, I.: Calcareous pancreatitis, Radiology 51: 214–218, 1948.
5. Reeves, R. J., and Moran, F. T.: Diffuse pancreatic calcification. An analysis of six
    cases, Radiology 51: 219–224, 1948.
6. Jaleski, T. C.: Pancreatic lithiasis, Ann. Int. Med. 20: 940–947, 1944.
7. Opie, E. L.: The relation of diabetes mellitus to lesions of the pancreas. Hyaline de-
    generation of the islands of Langerhans, J. Exper. Med. 5: 527–540, 1900.
8. Barron, M.: Relation of the Islets of Langerhans to diabetes with special reference to
    cases of pancreatic lithiasis, Surg., Gynec. and Obst. 31: 437–448, 1920.
9. Seegar, S. J.: Pancreatic lithiasis, Radiology 10: 126–138, 1928.
10. Edmondson, H. A., and Fields, I. A.: Relation of calcium and lipids to acute pancreatic
    necrosis, Arch. Int. Med. 69: 177–190, 1942.
11. Rienhoff, W. F., Jr., and Lewis, D.: Case of pancreatic lithiasis met with in Johns Hop-
    kins Hospital, Bull. Johns Hopkins Hosp. 54: 386–429, 1934.
12. Gillies, C. L.: Pancreatic lithiasis with report of a case, Am. J. Roentgenol. 41: 42–45,
    1939.
13. Sage, H. H.: Multiple diffuse pancreatic lithiasis; roentgen anatomy of the pancreas,
    Am. J. Roentgenol. 53: 28–32, 1945.

COCCIDIOIDAL MENINGITIS OF LONG DURATION: REPORT OF A CASE OF FOUR YEARS AND EIGHT MONTHS' DURATION, WITH NECROPSY FINDINGS *

By EDGAR ROSEN, M.D., and JOSEPH P. BELBER, M.D., *Oakland, California*

ALTHOUGH a sufficient number of cases of coccidioidal meningitis has now been published in the medical literature to merit consideration of this disease in all patients with obscure meningitides, the diagnosis can be readily overlooked unless it is kept in mind. The patient reported in this paper was not correctly diagnosed until his final hospital admission and his fifth year of illness, although he had been studied extensively in four other hospitals at various times since the start of his illness. Our main purposes in reporting this patient are to review the problems in diagnosis which he presented, and to stress the pertinent data which could have led to an accurate clinical appraisal early in the course of his disease.

The lengthy duration of this patient's illness is also a matter of considerable interest, since we were unable to find any published reports of cases surviving nearly this long. However, we have been informed by Dr. Charles E. Smith [15] of three unpublished cases with a duration of approximately four years each.

Although the endemic areas for coccidioidomycosis are limited in this country to certain regions of the West and Southwest,[14] widespread interest in the disease has been awakened in recent years. As a result of increased military and civilian travel, coccidioidal infections have been observed in areas far removed from endemic regions. An initial infection acquired in an endemic area may not pro-

duce manifest symptoms until after the affected individual reaches a location far distant from the site of infection. It has been noted that infection may occur merely as the result of travel by automobile or train through an endemic area.[16] In addition, unusual cases of infection have occurred due to spores transported from endemic areas in clothing or dusty shipments.[16]

Coccidioidomycosis is caused by the fungus *Coccidioides immitis*. Only the disseminated form of the disease (coccidioidal granuloma, progressive coccidioidomycosis) was recognized until a little over a decade ago, when Gifford and Dickson,[3,4,8] showed that *Coccidioides immitis* was also the cause of a much milder and more frequently observed infection ("Valley Fever") which was endemic in the San Joaquin Valley of California. Their discovery led to the realization that this benign form of coccidioidal infection and the far more serious coccidioidal granuloma were different stages of the same disease.

The parasitic phase of the organism is seen in the tissues of infected human or animal hosts, where it appears microscopically as a distinctive, doubly refractile spherule containing endospores. Reproduction in this phase takes place by rupture of the spherule and release of the endospores, which then go on to become new spherules.[4,20] The mycelial phase, noted in cultures of the organism and thought to exist in nature, produces chlamydospores and arthrospores which are highly infective. Ample evidence for the infective power of the spores has been furnished by the number of infections which have occurred in laboratory personnel.[16] Little is known concerning the reproductive cycle of the organism in nature, although successful soil cultures have been reported.[5,11] Emmons [5,7] has demonstrated the presence of the organism in wild rodents, and has suggested that rodents constitute a reservoir of the disease.

In the vast majority of human infections, the portal of entry is the respiratory tract, although occasional infection through lacerations or abrasions of the skin has been described.[2] Inhalation of infective arthrospores or chlamydospores by susceptible individuals is followed in one to three weeks by the initial or primary infection.[16] In approximately 60 per cent of infected persons, symptoms are entirely absent at this stage,[18] and indication of infection may hinge on the development of a positive coccidioidin skin test. When symptomatic, the usual picture of the primary infection is that of a bronchitis, pleuritis or pneumonitis,[17] and the symptoms often bear close resemblance to other respiratory infections caused by more commonly encountered etiologic agents. Cough, pleuritic chest pain, fever and other general constitutional symptoms are frequently observed. Hypersensitivity phenomena may also be present in some cases, such as erythema nodosum, arthritis or, less commonly, erythema multiforme or urticaria.[20] Examination of the blood reveals a definite increase of eosinophils in the majority of cases.[14,20] The coccidioidin skin test usually becomes positive shortly after the onset of the disease and remains positive for many years.[12]

In most instances, the disease is benign and self-limited. Usually the primary infection subsides completely, leaving no apparent sequelae and producing lasting immunity. In some cases, however, evidence of further active disease may result either from pulmonary complications of the primary infection or from dissemination. The pulmonary complications include cavitation, pleural effusion and, occasionally, spontaneous pneumothorax or hydropneumothorax.[16] Smith [16] emphasizes that these pulmonary lesions are not indicative of dissemination but that, on the contrary, pulmonary cavitation actually seems associated with re-

sistance to dissemination. He notes that in only one published case [9] has dissemination been reported in a patient with pulmonary cavitation.

The disseminated stage of the disease is characterized by varying degrees of spread which may affect practically any or all organs in the body. The pathologic changes are granulomatous in nature, and the disease frequently mimics various forms of systemic tuberculosis. When dissemination occurs it usually takes place early in the course of the disease, within a matter of weeks, infrequently after months, and rarely in the second year of the infection.[16] Once the disease becomes disseminated it assumes a far more malignant character, which is reflected by the mortality rate of 50 per cent.[16] Studies of military personnel showed that extrapulmonary dissemination occurred in one of 380 white males infected, and in 1 per cent of those with clinically recognized primary infections.[11] In Negro soldiers, the incidence of dissemination was found to be 10 times greater.[18]

Localization in the meninges characteristically produces a basilar meningitis with the histopathology of an infectious granuloma which contains the typical spherules of *Coccidioides immitis*. Although localization within nervous tissue is not the rule, discrete granulomatous lesions within the brain substance have been described, either with or without an accompanying meningitis.[1, 10] In addition to discrete intracerebral lesions, spread of the infection into nervous tissue may occur by direct extension from a meningitis.[10] It should also be noted that meningeal infection is not limited to the brain, but has also been described in the meninges of the spinal cord.[19]

Meningitis is quite frequent in disseminated coccidioidomycosis. Schlumberger [10] cites records at the Army Institute of Pathology which show that a basilar meningitis was found in 13 of 23 autopsied cases of coccidioidomycosis in which the brain and meninges were examined.

In some cases, meningitis may be the only sign of dissemination. Although the term "primary coccidioidal meningitis" has been occasionally employed to designate cases which show no other evidence of coccidioidal infection, this term is improper since it implies that the meningitis is a "primary" infection. It should be stressed that infection of the meninges with *Coccidioides immitis* invariably denotes dissemination.[15] No lesions of the disseminated stage occur without being preceded by a primary infection, which, as pointed out above, is practically always in the respiratory tract. However, the initial infection may be subclinical, or so mild as to escape notice, and evidence of this primary phase may have entirely disappeared by the time meningitis becomes apparent.

The diagnosis of coccidioidal meningitis will be discussed below in greater detail. However, it can be mentioned briefly here that methods are available which can conclusively establish the diagnosis, and that the disease can be recognized clinically on the basis of its general features, knowledge of previous geographic exposure, a history suggestive of an antecedent primary infection, and characteristic changes in the spinal fluid.

The prognosis of the disease is grave. No effective treatment is known, and a fatal termination is apparently inevitable. Of course the possibility cannot be denied that perhaps other cases may occur which escape diagnosis and recover, but no evidence for this is known. Only one apparent recovery from coccidioidal meningitis has been reported, by Sweigert et al.,[17] but information recently obtained from Dr. Sweigert [18] revealed that this patient died in April, 1947, four

years and two months after the onset of his original illness. The variable course of the disease and its occasional lengthy remissions make it hazardous to proclaim a cure without a long period of observation.

CASE REPORT

History: A 53 year old white male lineman was admitted to the Medical Service of the Veterans Administration Hospital, Oakland, California, on November 28, 1947, because of headache, weakness and mental confusion. These symptoms had been present intermittently since an attack of "encephalitis" in 1943. An adequate history could not be obtained from the patient, but additional information was secured from his wife and from abstracts of previous hospital records.

The patient was perfectly well until August, 1943, when he entered a hospital for an acute febrile illness accompanied by pleuritic pain in the anterior left lower chest. Physical examination was reported to be essentially negative except for "retraction of the left chest." The white blood cell count was 12,800, with 67 per cent polymorphonuclears and 12 per cent eosinophils. Roentgenogram of the chest showed increased prominence of the left hilum, which was reported as a "central pneumonia." The blood culture showed no growth in 14 days. The patient's symptoms subsided gradually and he was discharged one week after admission.

Eleven days later he was readmitted because of a chill and elevation of temperature. The chest roentgenogram then showed improvement in the appearance of the left hilum. A first strength tuberculin skin test performed at this time was positive. There was rapid improvement in the patient's condition and he was discharged in four days.

Three days after returning home, nausea, abdominal distress and fever necessitated readmission to the same hospital. Shortly after this admission he began to complain of severe headache. At this time slight stiffness of the neck was noted. Spinal taps were then performed for the first time, with the following findings reported in the spinal fluid: *Cell count:* 303 to 433 white blood cells per cu. mm. with 80 per cent lymphocytes. *Sugar:* 21.7 to 50 mg. per cent. *Pandy:* 2 plus. *Chlorides:* 770 mg. per cent. *Kolmer:* negative. *Colloidal gold:* negative. *Culture:* no growth in eight days. *Guinea pig inoculation:* negative for tuberculosis. Roentgenograms of the chest were now interpreted as negative. Blood counts showed slight leukocytosis with some eosinophilia (7 per cent and 10 per cent) in two of the four blood counts reported. Urinalysis was within normal limits. Negative agglutination tests were reported for typhoid, paratyphoid, brucellosis and tularemia.

The patient continued to complain of severe headache, and occasional episodes of nausea and vomiting occurred. Chills and fever were noted periodically. After one month in the hospital the patient's condition had not improved, and he was therefore transferred to a university hospital in a nearby city for further study.

Records forwarded from the latter hospital indicated that the spinal fluid then showed 100 to 200 cells (mostly lymphocytes), a total protein of 253 mg. per cent, a first zone colloidal gold curve, and a negative Wassermann. A positive neutralization test for equine encephalitis was reported at this time, but this was regarded with some skepticism because of the lack of conformity with the clinical picture. The patient was discharged after one month, with his illness still active and no diagnosis definitely established.

The patient was then reported to have developed marked mental confusion in addition to his other symptoms. Nine days after leaving the second hospital he entered a psychiatric institution, where he remained for the next 17 months. There the spinal fluid again showed a first zone elevation of the gold curve, low sugar, increased cells, and an elevated protein which ranged to 840 mg. per cent. Without

any specific therapy, the patient's illness finally showed slow improvement. In September, 1944, the spinal fluid showed a fall in the cell count to 12 white blood cells per cu. mm. and a fall in the protein to 93 mg. per cent; an abnormal gold curve persisted. In April, 1945, following a three month trial period at home, his condition was sufficiently improved to permit discharge.

There then followed a further period of convalescence at home for the next six months, during which the patient became entirely asymptomatic, regaining a completely normal personality and apparently perfect health. In September, 1945, he was sufficiently well to return to work as a lineman for a period of six months. At the end of this time his health again began to fail; his wife stated that "he started getting dizzy spells, upset and nervous, and headaches coming on him." This was soon followed by frequent vomiting and vague abdominal distress.

The above symptoms led to another hospital admission in April, 1946, his sixth admission and the fourth hospital in which he was studied. Complete investigation of the gastrointestinal tract was carried out because of the patient's abdominal symptoms. No conclusive diagnosis was established, although roentgen-ray studies were suggestive of an obstructing lesion at the pylorus, and a diagnosis of atrophic gastritis was entertained on the basis of a gastroscopic examination. The spinal fluid was reported as showing 8 white blood cells per cu. mm. and a protein of 150 mg. per cent. After hospitalization for approximately four months the patient was discharged unimproved.

After returning home in August, 1946, he still complained of frequent vomiting and occipital headache, but during the next few months he again showed moderate improvement. Although he did not fully regain his health, he did fairly well at home until September, 1947. At this time he once more began to go downward, with the onset of occipital headaches, marked weakness and mental confusion. Early in November, 1947, he experienced occasional urinary incontinence for the first time, and one mild convulsion which was followed by transient incoördination of the right hand. Progression of his illness finally necessitated admission to this hospital on November 28, 1947, when the patient came under our observation for the first time, in his fifth year of illness.

The remainder of the past history was noncontributory. Venereal disease was denied by the patient and his wife. There was no history of any familial neurologic disorders.

Physical Examination: On examination he appeared a well developed and well nourished middle aged white man who was extremely apathetic and too weak to stand or walk without assistance. He was well oriented but was confused regarding details of his illness. The temperature was 98.0° F., the blood pressure 112 mm. Hg systolic and 70 mm. diastolic, the pulse rate 68, and the respiratory rate 20. The heart and lungs were normal. The left pupil was slightly larger than the right, but the eyes were otherwise normal. The visual fields were normal when examined by the confrontation test. Despite the patient's general weakness, muscle strength did not appear to be greatly impaired. The tendon reflexes were hyperactive and approximately equal. No ankle clonus could be obtained. No tremors were present. There was poor performance of the heel-to-shin test bilaterally, but the finger-to-nose test was fairly well performed on either side. The abdominal and cremasteric reflexes could not be obtained. The left Hoffman and Babinski reflexes were definitely positive, and the right Babinski was equivocal. There was no demonstrable impairment of touch, pain, position or vibratory sensation. No nuchal rigidity was present. Other physical findings were not remarkable.

Roentgen-Ray and Laboratory Studies: The blood count and urinalysis were within normal limits. The blood Kahn was negative. The sedimentation rate was 11 mm. per hour (Westergren). The blood urea nitrogen was 12 mg. per cent. A

P.P.D. skin test (first test dose) was positive. The electrocardiogram was normal. The electroencephalogram showed slow medium to high voltage waves in all leads, and was interpreted as an abnormal tracing which was indicative of diffuse cortical involvement. Roentgenograms of the chest and skull were normal. Roentgenograms of the cervical and thoracic spine showed fairly marked hypertrophic changes but no other abnormality.

The initial lumbar puncture at this hospital was performed on December 1, 1947. Clear colorless fluid was obtained with a manometric pressure of 130 mm. H_2O. There were normal responses to bearing down and jugular pressure. The cell count was 12 white blood cells per cu. mm. with 10 lymphocytes and 2 polymorphonuclears. The globulin was 4 plus, and the total protein 720 mg. per cent. The Wassermann was negative, and the colloidal gold curve 5555555321.

Course in the Hospital: During the first month of hospitalization the patient's condition grew steadily worse. His mental confusion increased and he became progressively more listless and stuporous. Shortly after admission, he began having clonic convulsive seizures which recurred periodically for about three weeks. Occasional urinary incontinence was noted, and on one occasion catheterization was required because of inability to void. Vomiting occurred fairly often, and the patient soon began to experience difficulty in swallowing.

The temperature remained normal except for an occasional slight rise to a maximum of 99.6° F. During this period, therapy was entirely symptomatic. Tincture of belladonna, Rabellon and phenobarbital were of no apparent benefit.

Along with the patient's downward course, the abnormal findings in the spinal fluid became more marked. Spinal fluid obtained on December 18, 1947, was still colorless and under normal pressure. The cell count was 22 white blood cells per cu. mm. (20 lymphocytes, 2 polymorphonuclears), the sugar 60 mg. per cent, chlorides 750 mg. per cent, and total protein 1090 mg. per cent. On December 29, 1947, the spinal fluid appeared xanthochromic. Laboratory analysis revealed a total protein of 1800 mg. per cent, a 5555555555 colloidal gold curve, and 1 lymphocyte per cu. mm.

There was also progression of the neurologic signs. After several weeks the Hoffman and Babinski reflexes were definitely positive bilaterally, and reëxamination of the fundi revealed that several retinal hemorrhages had now appeared. At no time was any definite nuchal rigidity noted.

Diagnosis: The diagnosis was obscure at the time of admission. It was originally felt that his symptoms might possibly be caused by a degenerative process secondary to viral encephalitis. When the high spinal fluid protein was reported, and further information became available concerning the patient's original sickness in 1943, the diagnosis of a postencephalitic state appeared untenable. An intracranial neoplasm was one possibility to be considered, but was not favored because of the febrile and vacillating course of the patient's illness, including partial and complete remissions lasting up to a year. Syphilis was excluded by the lack of a history of lues, the spinal fluid protein, and the negative blood and spinal serologic tests. Tuberculosis was judged most unlikely because of the long course, the remissions, the absence of pulmonary lesions, and examinations of the spinal fluid at other hospitals which had proved negative for tuberculosis. Thus a search for other chronic granulomas was begun, especially those of fungus or protozoal origin, with initial consideration being given to the possibility of a coccidioidal meningitis. Accordingly, a coccidioidin skin test was performed which was positive in 1 : 100 dilution. In addition, a specimen of the patient's blood was sent to Dr. Charles E. Smith, at the Stanford University School of Medicine, for serologic tests for coccidioidomycosis.

The circumstances under which the diagnosis was finally established are worthy of comment. On January 13, 1948 (before the serologic studies were performed),

Dr. Smith visited this hospital and had an opportunity to interview the patient and his wife. It was then learned that, although they had not lived in any endemic area for coccidioidal infections, they had taken a trip to Bakersfield, California, about August 1, 1943, three weeks before the initial illness began, and had remained there overnight. Bakersfield lies in the San Joaquin Valley, and is a known endemic area for coccidioidomycosis. On the basis of this geographic exposure, the three week incubation period, the hilar enlargement noted at the onset of illness, the high spinal fluid protein, the first zone gold curve, and the positive coccidioidin skin test, Dr. Smith made a conclusive diagnosis of coccidioidal meningitis.

Confirmation was soon given to this diagnosis by the results of serologic testing and isolation of the organism from the spinal fluid. Complement fixation tests on blood and spinal fluid obtained January 15, 1948 (see table 1 below), conclusively indicated the presence of a coccidioidal meningitis. In addition, culture of the spinal fluid obtained the same date showed growth of *Coccidioides immitis* in eight days in a culture medium consisting of brewer's thioglycollate and tryptose semisolid agar.

TABLE I

Serologic Tests for Coccidioidal Infection*
Complement Fixation Tests: Serial Dilutions of Serum (0.25 c.c.)

	Specimen Obtained	1:2	1:4	1:8	1:16	1:32	1:64
Serum	Jan. 15, 1948	++++	+++	++	0	0	0
Spinal fluid	Jan. 15, 1948	++++	++++	++++	++++	+++	Not done

Conclusion: Never before have we seen spinal fluid coccidioidal complement fixation so much higher than that of serum. This certainly clinches diagnosis of coccidioidal meningitis.
* Facilities of the coccidioidomycosis study, Commission on Acute Respiratory Diseases, Army Epidemiological Board at Stanford Medical School.

Remainder of Hospital Course: The convulsions and vomiting gradually subsided, but the patient continued to exhibit marked lethargy and confusion. There was intermittent difficulty in swallowing, requiring the occasional administration of parenteral fluids. Therapy was entirely supportive except for a trial of penicillin which was of no apparent benefit. During the second month of hospitalization the patient began to have a low grade fever which continued throughout the remainder of his course, with the temperature occasionally spiking to about 102° F. After several months his extreme lethargy led to the development of several large decubitus ulcers, which were at first suspected of being disseminated lesions of coccidioido-mycosis. However, culture of pus obtained from these areas was negative for *Coccidioides immitis*, and roentgen-ray studies of the underlying osseous structures showed no evidence of bony destruction. Urinary abnormalities became evident during the third hospital month, with moderate numbers of white blood cells and albumin in repeated urine samples. Urine cultures were repeatedly negative for fungi. Three blood cultures showed no growth.

The spinal fluid continued to show findings essentially similar to those noted above until March 8, 1948. Analysis of spinal fluid obtained on this date showed a fall in the total protein to 380 mg. per cent, and in the cell count to zero. Serologic testing of the same spinal fluid showed a distinct fall in complement fixation titer. However, spinal fluid obtained three weeks later (March 30, 1948) again showed a marked rise in the total protein to 1300 mg. per cent, and a rise in the complement fixation titer which led Dr. Smith to comment that the "outlook is grim."

This prediction of a "grim outlook" was soon proved correct. On April 21, 1948, the patient was noted by his wife to have suddenly become cyanotic, and

she promptly summoned a physician (E. R.) to the bedside. On examination it was obvious that the patient was moribund. He was deeply cyanotic and no respiratory movements were discernible. The pulse was of poor quality, but the heart tones were fairly good and the cardiac rhythm was regular. Artificial respiration, oxygen by mask and intravenous caffeine sodium benzoate were immediately administered but were of no avail. The heart sounds became progressively fainter and more irregular, and ceased entirely in approximately three minutes. Death was apparently respiratory.

Postmortem Examination: Autopsy was performed by Dr. Bruno Gerstl. The striking features of the necropsy findings included an extensive basilar meningitis,
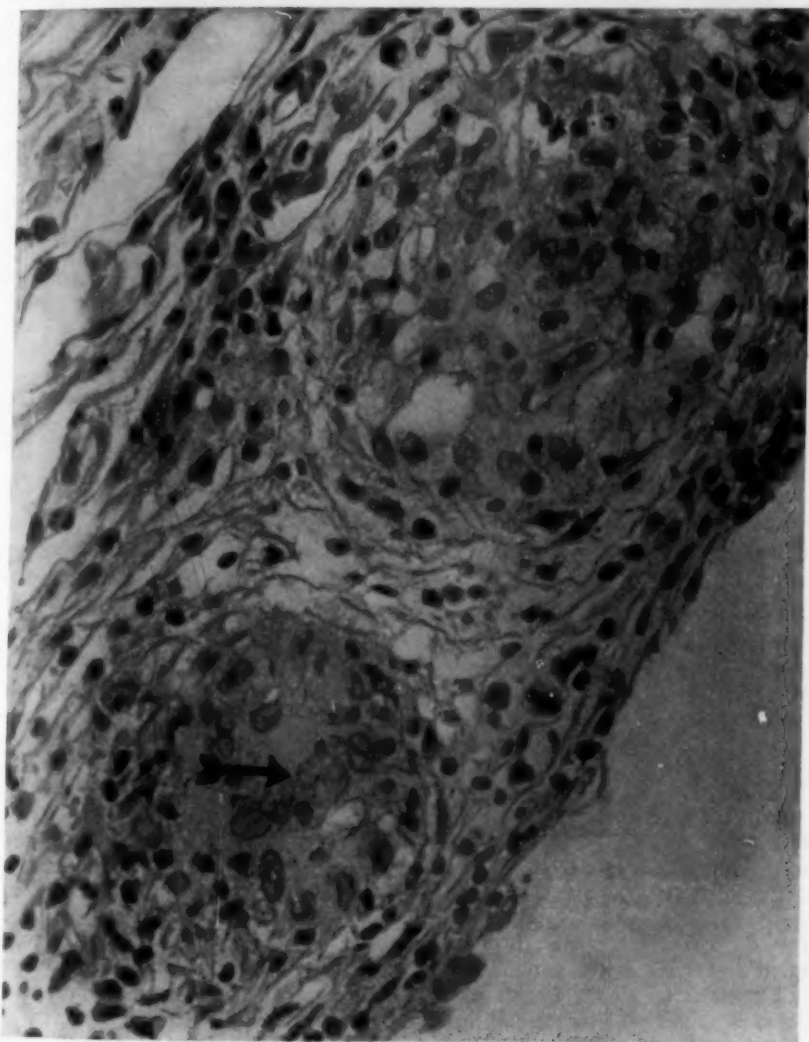
FIG. 1. Granulomatous changes in pia-arachnoid. A spherule of *Coccidioides immitis* (marked by arrow) is seen within a large giant cell (× 400).

ependymitis, and evidence of previous primary coccidioidal infection in the hilar lymph nodes.

Brain: Upon opening the skull a large amount of cloudy subdural fluid escaped. Thick yellowish-white exudate was present over the entire base of the brain, including the interpeduncular and basilar cisterns. The convolutions appeared flattened, particularly over the convexities of the hemispheres, and the sulci were somewhat
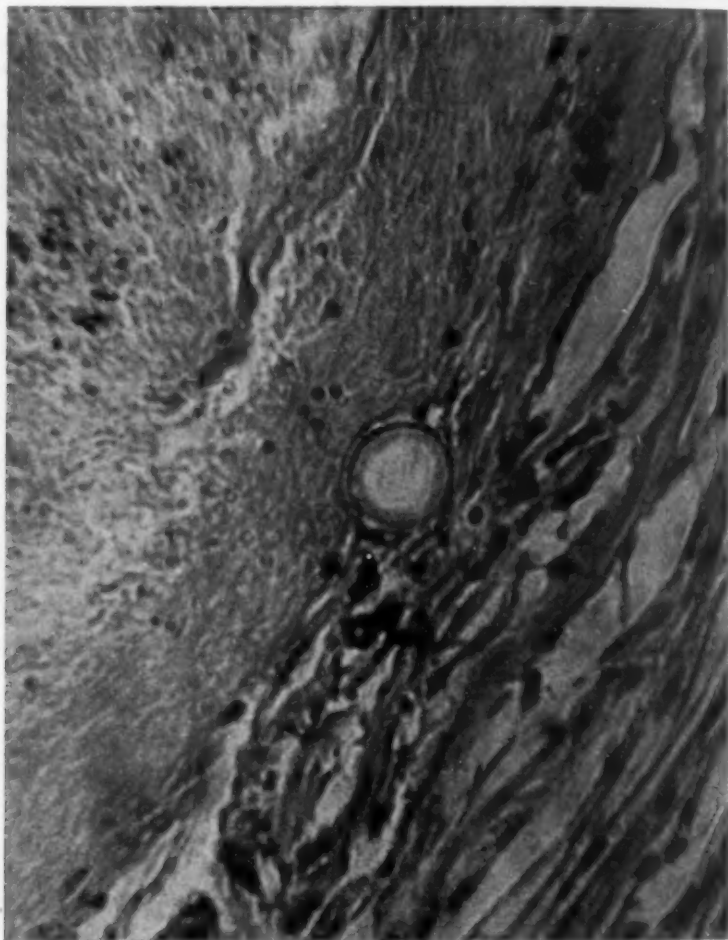
FIG. 2. A spherule of *Coccidioides immitis* seen in the peribronchial tissue of a large bronchus (× 450).

narrowed. Frontal sections through the hemispheres, brain stem and cerebellum revealed a variable gritty, ground-glass appearance of the ependymal lining throughout all ventricles. In the fourth ventricle there were small, almost peduncular projections, measuring 0.5 to 1.0 mm. in diameter. The choroidal plexus in each lateral ventricle was firmly adherent to the ependymal lining. There were no gross changes in the cortical gray matter or in any of the parenchymal subsurfaces, including the brain stem and cerebellum.

On microscopic examination, the pia-arachnoid showed an extensive exudate composed of small round cells and a moderate number of plasma cells. Occasionally there were noted large multinucleated giant cells which contained a large, round, thick-walled spherule within which there were endospores (figure 1). A number of small granulomatous lesions were also found in the ependyma of the ventricles, containing similar spherules within giant cells.

Lungs: Both lungs were inflated with formalin prior to sectioning. There were no gross changes in the parenchyma except for a small area of atelectasis in each lower lobe. A hilar lymph node at the root of the left upper lobe bronchus contained three whitish, moderately firm areas on its surface, in addition to anthracotic changes. A lymph node of similar appearance was found at the root of the right upper lobe bronchus.

Microscopic examination of the hilar lymph nodes revealed round to oval areas of colliquation necrosis surrounded by fibrous tissue proliferation. No spherules were found in these areas. However, a granulomatous lesion of microscopic size was found in the peribronchial tissue of a large bronchus, containing numerous large mononuclear cells, fibroblasts, and connective tissue at the periphery. One of the mononuclear cells in this area contained a spherule (figure 2), consisting of a highly refractile capsule surrounding a faintly pink-staining inner area. No endospores were visible within the capsule. The finding of this spherule in combination with the changes in the hilar lymph nodes was interpreted as indicating previous coccidioidal infection in these areas.

The remainder of the postmortem examination failed to reveal any evidence of coccidioidomycosis elsewhere in the body. Examination of the spinal cord was unfortunately omitted. Other incidental findings included two large decubitus ulcers which failed to show any microscopic evidence of coccidioidomycosis, some passive congestion of the liver and spleen, and moderate sclerotic changes in some of the large arteries.

DISCUSSION

When the diagnosis was finally established, it was at once evident that this patient's illness was in every way classical for a primary coccidioidal pulmonary infection followed by early dissemination to the meninges and a chronic meningitis of long duration. A visit, albeit short, to an area where coccidioidomycosis is endemic was followed in three weeks by a typical primary infection, characterized mainly by fever, pleuritic chest-pain, abnormal prominence of the left hilum by roentgenogram, and eosinophilia of 12 per cent in the peripheral blood. Meningeal localization was clearly apparent one month later, when severe headache and slight nuchal rigidity were noted. At this time respiratory symptoms and the abnormality in the chest roentgenogram had disappeared, and no further clinical or roentgen-ray evidence of pulmonary involvement reappeared at any time, although necropsy examination more than four and a half years later disclosed histologic evidence of previous coccidioidal infection in the hilar areas.

The early involvement of the central nervous system was then followed by a lengthy course which included variable periods of improvement and exacerbation, and a complete remission in the third year of illness lasting for approximately one year. Death finally occurred four years and eight months after the onset of illness. Extensive diagnostic studies performed in different hospitals failed to reveal the nature of the patient's disease until a specific search was made for coccidioidomycosis in the fifth year of illness. The diagnostic spectrum is perhaps best illustrated by the galaxy of diagnoses which were found in the records of previous

hospitalizations : bronchopneumonia, central, left ; bronchopneumonia, residual of ; lymphocytic choriomeningitis ; equine encephalitis ; psychosis with encephalitis ; residuals of leptomeningitis ; atrophic gastritis.

The antemortem diagnosis of coccidioidal meningitis is not difficult if the disease is considered and appropriate studies are performed. When coccidioidal meningitis is part of a widely disseminated infection, biopsy or culture of readily accessible lesions usually brings to light the etiologic agent, and it may be inferred that any neurologic symptoms present are due to the same organism. In cases with dissemination only to the meninges and no accessible lesions elsewhere, the diagnosis cannot be readily made without specific consideration of coccidioidomycosis, especially if the primary infection has been unrecognized. Such a patient presents a problem in differential diagnosis which embraces many possibilities, such as brain tumor, degenerative diseases of the brain, and infectious diseases including brain abscess, viral encephalitis, neurosyphilis, and particularly tuberculous meningitis or infection of the central nervous system with protozoa or other fungi. The methods outlined below will be helpful in establishing the diagnosis.

The history may be of inestimable value, especially the geographic history, if presence in an endemic area, no matter how fleeting, can be established. The occurrence of respiratory symptoms or erythema nodosum shortly thereafter is particularly suggestive, although one must remember that the primary infection may have been subclinical. The course is subject to considerable variation, but usually one expects a smoldering, protracted course, subject in some instances to remissions and exacerbations. Symptoms and physical findings are not characteristic and depend upon the localization of lesions. Headache, nuchal rigidity, stupor, weakness and mental changes may be encountered, as well as evidence of more localized central nervous system involvement. Fever may or may not be present, depending on the activity of the disease process. Routine laboratory findings are nonspecific.

Spinal fluid examination usually reveals characteristic abnormalities which strongly suggest the possibility of coccidioidal meningitis. The important diagnostic features of the spinal fluid are illustrated in table 2 which shows the spinal fluid findings in our patient. Smith [14, 15] has particularly emphasized the importance of a "paretic" gold curve as a diagnostic clue. Characteristically, there is marked elevation of the spinal fluid protein, which ranged to 1,800 mg. per cent in this case. The spinal fluid sugar tends to be low, as in other infectious meningitides other than those of viral etiology. The cell count is variable, with lymphocytes constituting the majority of the cells. Of those polymorphonuclear cells which are present, there frequently are proportionately high numbers of eosinophils when stained smears are examined.[14, 19]

Isolation of the organism from the spinal fluid by animal inoculation or culture of course establishes the diagnosis without further ado, but unhappily the organism is frequently elusive and repeated efforts to recover it may be fruitless even in the presence of an active meningitis, thus precluding dependence on culture as a means of diagnosis. In our case we were fortunate in obtaining a positive spinal fluid culture on one occasion, after the diagnosis had already been established by serologic tests, but numerous cultures in the past had been negative.

A positive skin test with 1 : 10 or 1 : 100 coccidioidin may be found. It indicates infection in much the same manner as a tuberculin skin test, and is not an

TABLE II

Summary of Spinal Fluid Reports, Based on Final Hospitalization and Available Data from Previous Hospital Records

Date	Oct. 3, 1943 to Oct. 18, 1943	Oct. 21, 1943 to Nov. 20, 1943	Dec. 7, 1943	Dec. 14, 1943	May 26, 1944	June 19, 1944	July 1, 1946	Dec. 1, 1947	Dec. 18, 1947	Dec. 29, 1947	Jan. 15, 1948	Jan. 21, 1948	Feb. 3, 1948	Feb. 11, 1948	Mar. 8, 1948	Mar. 30, 1948
Color				Clear	Xantho-chromic	Slightly xantho-chromic		Clear colorless	Clear colorless	Xantho-chromic	Xantho-chromic	Xantho-chromic	Xantho-chromic	Xantho-chromic	Slightly xantho-chromic	Xantho-chromic
Cells	303 to 433 80% L*	100 to 200 Mostly L*	26	29	162 98% L	219	8	12 83% L	22 91% L	One L		6 L	3 L	2 L	0	6 L
Globulin	++		+++	++	++++	++++		++++		++++		++++	++++		++++	+++
Protein		253	210	194	600	840	150	720	1,090	1,800		1,390	950	900	380	1,300
Sugar	21.7 to 50	38		20	23				60	75				52	66	76
Chloride	770	603							750							
Colloidal gold	00000-00000	"Paretic"	44555-44321	45554-43211	55555-55554	55555-55555		55555-55321		55555-55555	55555-55555	55555-55555	55555-55443		55555-54432	

* Lymphocytes.

index of activity.　Although a positive reaction may be helpful in diagnosis, a negative result by no means excludes the disease, as sensitivity to coccidioidin may be low or absent in the presence of disseminated infection.[14]

Serologic studies approach a high degree of specificity.　Blood complement fixation and precipitin tests in significant titers definitely indicate activity, and in high titers may strongly suggest dissemination.　Spinal fluid complement fixation tests are thought to be positive only in the presence of active meningitis, and it is unusual in such circumstance that they are negative, although they may be late in developing.[15]　It is important to stress that a conclusive diagnosis of coccidioidal meningitis can be made on the basis of significant amounts of complement fixing antibody in the spinal fluid.　It should also be emphasized that the value of this test is not limited to diagnosis, as serial determinations are helpful in judging prognosis.　The value of the test in this respect was effectively demonstrated to us by the death of our patient shortly after the forecast of a "grim outlook" on the basis of a rise in the complement fixation titer in the spinal fluid.

SUMMARY

1. A case report of coccidioidal meningitis of four years and eight months' duration is presented, with clinical and necropsy findings.　This is the longest reported duration for this disease.

2. The correct diagnosis was not established until the fifth year of illness, despite extensive study during six previous periods of hospitalization in four different hospitals.　Nevertheless, analysis of the patient's history and earlier hospital records revealed sufficient clinical and laboratory data to justify a clinical diagnosis of coccidioidal meningitis at an early stage of his disease.

3. The subject of coccidioidomycosis is briefly reviewed, with particular stress on the diagnostic features of coccidioidal meningitis, and the methods of establishing this diagnosis.

BIBLIOGRAPHY

1. Abbott, K. H., and Cutler, O. I.: Chronic coccidioidal meningitis, Arch. Path. 21: 320-330, 1936.

2. Dickson, E. C.: Coccidioides infection, Part I, Arch. Int. Med. 59: 1029-1044, 1937.

3. Dickson, E. C.: Valley fever, California and West. Med. 47: 151-155, 1937.

4. Dickson, E. C., and Gifford, M. A.: Coccidioides infection (coccidioidomycosis), II, Arch. Int. Med. 62: 853-871, 1938.

5. Emmons, C. W.: Isolation of coccidioides from soil and rodents, Pub. Health Rep. 57: 109-111, 1942.

6. Emmons, C. W., and Ashburn, L. L.: The isolation of *Haplosporangium parvum* N. Sp. and *Coccidioides immitis* from wild rodents, Pub. Health Rep. 57: 1715-1727, 1942.

7. Emmons, C. W.: Coccidioidomycosis in wild rodents, Pub. Health Rep. 58: 1-5, 1943.

8. Gifford, M. A.: Annual Report Kern County Health Department for the Fiscal Year July 1, 1935, to June 30, 1936, pp. 22-23.

9. Kurz, E. R. H., and Loud, N. W.: Coccidioidomycosis in New England, New England J. Med. **237**: 610–616, 1947.

10. Schlumberger, H. G.: A fatal case of cerebral coccidioidomycosis with cultural studies, Am. J. M. Sc. **209**: 483–496, 1945.

11. Stewart, R. A., and Meyer, K. F.: Isolation of *Coccidioides immitis* from the soil, Proc. Soc. Exper. Biol. and Med. **29**: 937–938, 1932.

12. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**: 790–807, 1943.

13. Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G.: Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases, Am. J. Pub. Health **36**: 1394–1402, 1946.

14. Smith, C. E.: Recent progress in pulmonary mycotic infections, California Med. **67**: 179–185, 1947.

15. Smith, C. E.: Personal communication.

16. Smith, C. E., Beard, R. R., and Saito, M. T.: Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation, Ann. Int. Med. **29**: 623–655, 1948.

17. Sweigert, C. F., Turner, H. W., and Gillespie, J. B.: Clinical and roentgenologic aspects of coccidioidomycosis, Am. J. M. Sc. **212**: 652–673, 1946.

18. Sweigert, C. F.: Personal communication.

19. Whims, C. B.: Coccidioidal meningitis, Bull. U. S. Army M. Dept. **7**: 1947, vii, 466–471, 1947.

20. Willett, F. M., and Weiss, A.: Coccidioidomycosis in Southern California, Ann. Int. Med. **23**: 349–375, 1945.

DEATH FOLLOWING STERNAL PUNCTURE: REPORT OF TWO CASES *

By JOSEPH G. FORTNER, M.D., and EMMA S. MOSS, M.D., F.A.C.P.,
New Orleans, Louisiana

THE relatively simple procedure of sternal puncture for marrow aspiration may be the cause of death. A review of the literature reveals four reported cases of death following this procedure.[1,2,3] It is the purpose of this communication to record two additional cases and to comment upon the symptomatology and the mechanism of death.

CASE REPORTS

Case 1. A 23 year old colored female was admitted to Charity Hospital on June 25, 1948, complaining of a sore throat and tender gums of three months' duration. Hematologic studies of the peripheral blood and bone marrow revealed an acute leukemia. Aminopterin was begun on July 1, 1948. Progressively severe anemia and leukopenia ensued.

On July 17, 1948, a sternal marrow aspiration was performed in the routine manner. The skin and subcutaneous tissues were infiltrated with 1 c.c. of 2 per cent procaine solution. Using an 18-gauge spinal needle, the external sternal lamina was perforated after considerable difficulty. The sensation of decreased resistance which usually accompanies perforation of the external sternal lamina was experienced. On aspiration, however, blood could not be obtained. The needle was withdrawn slightly

and a small amount of fluid was aspirated. This proved to be peripheral blood. The patient suddenly became pale and began to perspire profusely. Subsequently, the eyeballs rotated upward, the body became rigid, and slow thrashing movements of the lower extremities began. The upper extremities remained quiet. The patient then became opisthotonic and developed respiratory difficulty. The opisthotonos gradually subsided and the respirations, which were long and sighing in type, decreased in frequency. The pulse could not be palpated and respirations gradually ceased in spite of the administration of coramine, intracardiac adrenalin and artificial respiration. The entire episode lasted less than 10 minutes. The clinical impression at the time of death was cardiac failure resulting from a reaction to procaine.

Necropsy Findings: Necropsy revealed an asthenic type of chest. There was a

Fig. 1. Photograph of the opened, fixed heart demonstrating the 0.6 cm. laceration in the anterior wall of the pulmonary conus. This laceration penetrated into the right ventricular chamber.

needle puncture wound in the midsternum at the level of the third intercostal space which passed completely through the sternum. Otherwise, the sternum appeared grossly normal. There was a normal disposition of the intrathoracic structures.

The pericardium was thin, smooth and glistening. The pericardial sac contained approximately 300 c.c. of partially clotted blood which distended the sac to the right and left. A longitudinal slit-shaped wound in the pulmonary conus, just below the pulmonary ring, penetrated into the right ventricular chamber. The wound measured 0.6 cm. in length. There was a subepicardial area of ecchymosis, 2 cm. in diameter, at the apex of the left ventricle. This was the site of the intracardiac adrenalin injection (figure 1). Otherwise the heart was normal.

At necropsy an experimental sternal puncture was performed on the sternum, which had been removed. On perception of the sensation of decreased resistance

usually accompanying penetration of the tip of the needle through the external sternal lamina, it was found that the needle had pierced the entire sternum and its tip was seen to extend approximately 3 mm. beyond the internal sternal lamina.

The anatomic diagnoses were: Penetrating wound of the skin, sternum, pericardium and right ventricular myocardium; intrapericardial hemorrhage; cardiac tamponade; acute leukemia.

Case 2. A 68 year old colored male was admitted to Charity Hospital on September 14, 1946. He complained of a cough of one month's duration, dyspnea, weakness, palpation, substernal discomfort, and joint pains of six months' duration. This patient was moderately well nourished and did not appear acutely ill. The pulse was 92 and the blood pressure 110 mm. Hg systolic and 65 mm. diastolic. The heart was of normal size to percussion. There were a systolic murmur at the apex and a soft systolic murmur at the base. The physical examination was otherwise essentially negative.

Examination of the peripheral blood revealed a hemoglobin of 4.7 gm. per cent and an erythrocyte count of 0.55 million per cubic millimeter. The anemia improved slightly after a blood transfusion. An electrocardiogram revealed auricular bigeminy but was otherwise within normal limits. There was no essential change from one taken three years previously. Roentgen examination of the chest revealed a cardiac-thoracic ratio of 15.2 to 27.8. There was no evidence of pulmonary disease.

On September 24, 1946, a sternal marrow aspiration was performed. The skin and subcutaneous tissue were infiltrated with 2 c.c. of 1 per cent procaine solution. Considerable difficulty was encountered in penetrating the outer sternal lamina. However, 1.25 c.c. of red fluid marrow was withdrawn. The patient suddenly became opisthotonic, with mild clonic and tonic convulsions. Passage of gas per rectum and involuntary passage of urine followed. The respirations slowed to two to six per minute and became labored and gasping in nature. The pulse and heart sounds were weak but regular. The blood pressure could not be obtained. One centimeter of caffeine sodium benzoate was given subcutaneously and artificial respiration was administered. Slight response was evidenced by the return of corneal reflexes and conjugate movements of the eyes. Both pupils were round, equal and of normal size. The respirations increased in frequency and the neck veins became tremendously engorged. Heart action and respirations ceased at approximately the same time and some 30 minutes after administration of the procaine. Clinical impression at the time of death: fatal procaine reaction. Permission for necropsy could not be obtained.

The marrow obtained just prior to death contained 95 to 98 per cent granulocytic cells but no erythrocytic elements. A diagnosis was made of aplastic anemia of undetermined etiology.

The similarity of the two cases is striking. The patients were anemic and chronically ill; there was unusual difficulty in obtaining a satisfactory aspiration; the clinical symptoms were very similar, and death occurred within 30 minutes after the sternal puncture; the clinical impression in both cases was death due to a procaine reaction.

DISCUSSION

In 1944, Meyer and Halpern [1] first reported a death following sternal puncture. Their patient was a 51 year old man with chronic myelocytic leukemia, severe anemia and heart disease. Two previous attempts at marrow aspiration had been made. At the time of death one attempt was unsuccessful, but a

second, at a slightly different level, yielded a few drops of marrow. Hematologic
studies revealed a chronic myelocytic leukemia.

Immediately after removal of the needle the patient became faint, dyspneic
and cyanotic, and had a rapid, feeble pulse. The neck veins became distended
and the blood pressure was not obtainable. Death occurred within a few min-
utes. The patient experienced no unusual pain during the procedure. A ter-
minal electrocardiogram revealed bizarre ventricular complexes indicating severe
conduction defects with progressive bradycardia until asystole was complete.
They believed this to be due to a fatal cardiac inhibitory reflex initiated by fear
and mediated through the vagus. Permission for an autopsy could not be
obtained.

Scherer and Howe [2] in 1945 reported a death following sternal puncture in
a 31 year old white male who had a malignant teratoma of the anterior medi-
astinum and a severe anemia. At the time of death, attempted marrow aspira-
tion at several levels yielded only a small amount of blood-tinged fluid. Several
previous attempts had been unsuccessful. Shortly after completion of the aspira-
tion, the patient became pale and semicomatose. The pulse was thready and
rapid, the blood pressure was unobtainable, the pupils were dilated, and the
respirations were noisy. The patient died approximately 30 minutes after the
aspiration and within a few minutes of onset of the symptoms.

Necropsy revealed a normal intrathoracic disposition of structures and a
penetrating needle puncture wound of the sternum and pericardium. The peri-
cardial sac contained 350 c.c. of fresh blood. There was a triangular laceration
of the musculature of the right ventricle which did not penetrate into the ven-
tricular cavity. No injury of the coronary vessels was found. Section of the
sternum revealed anaplastic tumor tissue which had replaced the marrow.

Bardham [8] in 1947 reported two cases of death following sternal puncture.
In the first, a marrow aspiration was attempted in an effort to confirm a diag-
nosis of kala-azar. On insertion of the needle the patient gasped, rapidly went
into shock, and died within three minutes. The clinical picture resembled that
of pulmonary embolism. Necropsy revealed a penetrating puncture wound in
the sternum beneath which was a laceration three-quarters of an inch long in
the anterior wall of the right ventricle. Death was due to a hemopericardium
with cardiac tamponade. Other findings were those of early kala-azar.

In the second case, a marrow aspiration was performed in the study of an
anemia. Upon insertion of the needle, the patient gasped and went into shock.
Death occurred in approximately four minutes. Necropsy revealed a laceration
seven-eighths of an inch long in the right ventricle and a hemopericardium.
A needle guard was used in both instances.

SYMPTOMATOLOGY

The clinical and pathologic findings associated with this complication of
sternal puncture may be summarized as follows:

1. The patient is usually chronically ill, anemic and debilitated.
2. No unusual discomfort is experienced by the patient during the procedure.
3. Difficulty is often encountered in performing the sternal puncture, and
   there may be a history of previous unsuccessful attempts.
4. On aspiration, marrow may or may not be obtained.

5. On withdrawing the needle, a group of signs and symptoms occur which
   are characteristic of a rapidly developing interference with cardiac filling
   and a rapidly failing circulation with cerebral anoxia: faintness, pallor,
   profuse sweating, cyanosis, progressive dyspnea, a rapid, feeble pulse, an
   unobtainable blood pressure, and distention of the neck veins. As the
   circulatory failure progresses, the signs of severe cerebral anoxia may
   develop: opisthotonos, tonic and clonic movements of the extremities, and
   eye changes.
6. Death usually occurs within five to 10 minutes, but may be delayed for
   approximately one-half hour.

Pathologically, this syndrome is characterized by a tear in the anterior wall
of the right ventricle which may involve only the superficial ventricular muscu-
lature or may penetrate into the ventricular cavity. The resultant hemoperi-
cardium causes mechanical cardiac arrest.

MECHANISM OF DEATH

It would seem that death immediately following sternal puncture for marrow
aspiration, as reported thus far, is caused by penetration of the needle through
the sternum, with laceration of the right ventricle, intrapericardial hemorrhage
and cardiac tamponade. The sequence of events appears to be as follows: On
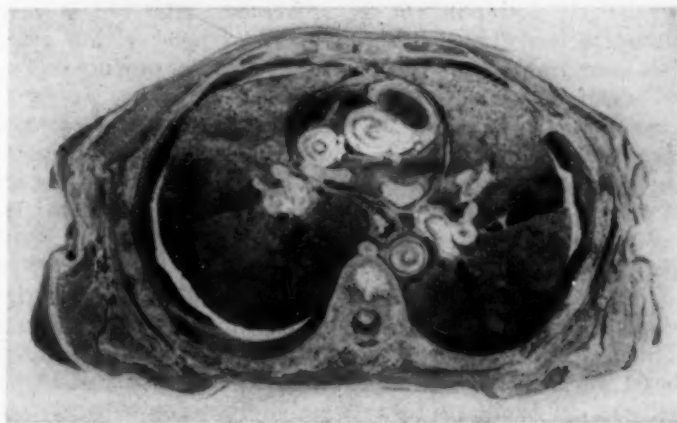
FIG. 2. Transverse section through the thorax of a cadaver at the level usually chosen
as the site for sternal marrow aspiration. Note the narrowness of the anterior mediastinal
space, even though the organs have been fixed, which would tend to shrink the viscera and
increase the depth of the space.

insertion of the needle, the operator is unaware of the true depth of the needle's
point. This may be due to pathologic changes in the bone of the sternum, an
abnormally thin sternum, or difficulty in obtaining a marrow specimen. The
needle pierces the posterior sternal lamina and the apposed heart.

The apposition of the sternum and heart is the result of two mechanisms:
the inward movement of the sternum, and the motion of the heart. The body
of the sternum is displaced posteriorly as force is exerted in the performance of

the puncture (figure 2). During systole the heart rotates to the right and moves anteriorly, striking the chest wall. The middle layer of myocardial fibers is attached to the pulmonary ring, and their contraction pulls the left and right ventricles forward and to the right. The force of myocardial contractions may be increased in apprehensive patients.

When the needle penetrates and protrudes beyond the sternum, the apposed heart may be pierced and a slit-shaped wound in the heart's wall result. The shape of the wound is due to the to-and-fro motion of the heart against the protruding fixed needle. This to-and-fro movement of the heart results from the contraction and relaxation of the superficial and deep layers of the myocardium which alternately shorten and lengthen the ventricles.

Although the opening produced may be small, blood pours into the pericardial sac with each systole. Since the rise in intrapericardial pressure is acute, the pericardial sac is placed under tension but is not greatly enlarged. The heart may decrease slightly in size. As the intrapericardial pressure reaches and finally exceeds the venous pressure, the chamber of the heart can no longer fill with venous blood. The pulse pressure decreases, the heart rate increases, and the heart sounds become muffled and indistinct. The great veins become distended with blood; cyanosis, sighing, irregular respirations, pallor, sweating and other manifestations of a failing circulation appear. Cerebral anoxia develops before death ensues.

If the ventricular musculature is only superficially lacerated, the outpouring of blood is relatively slower than if the entire ventricular wall is pierced. The symptoms may be less dramatic, and a greater length of time elapses before death. It is conceivable that a tamponade could be produced if a coronary vessel were lacerated.

Extensive traumatic laceration of the myocardium and therapeutic cardiac puncture are not incompatible with life. Therapeutic cardiac punctures are made through the soft tissues of the chest wall near the apex of the heart. The needle is not fixed by bone, and moves with the motion of the heart. A small puncture wound is produced, rather than a laceration. Even so, some bleeding into the pericardial cavity does occasionally occur. Nonfatal wounds of the myocardium cause bleeding into the pericardial sac, but hemorrhage may be arrested by clot formation and contraction of the musculature before a tamponade occurs. There are undoubtedly instances in which the needle has penetrated into the heart during a sternal puncture and the patient has experienced no untoward effect. In debilitated patients and those with prolonged clotting times, the clotting mechanism may be ineffective, and if the sternum is perforated and a laceration of the myocardium occurs, a fatal tamponade is more likely to result.

PREVENTION AND TREATMENT

It is our belief that the sternum is not the most desirable site for marrow aspiration. The iliac crests, transverse vertebral processes and the greater femoral trochanter are as satisfactory and much safer. In children less than five years of age, the tibia offers an excellent site.

If the sternum is chosen as the site for marrow aspiration and a tamponade occurs, the blood should be aspirated rapidly from the pericardial sac while arrangements are made for immediate surgical repair of the myocardium.

CONCLUSION

Two case reports of death following sternal puncture are added to the four previously reported in the literature.   Sternal marrow aspiration is not always an innocuous procedure.   Even though a guard is used, the needle may transverse the sternum, lacerate the myocardium, and cause cardiac tamponade.   The laceration in the myocardium is usually a linear tear produced by the motion of the heart against the stationary point of the needle protruding through the sternum.   The symptoms produced are those of rapid circulatory failure and cerebral anoxia.

It is urged that a site other than the sternum be chosen for marrow aspiration, i.e., the iliac crest.

BIBLIOGRAPHY

1. Meyer, L. M., and Halpern, J.: Death following sternal puncture, Am. J. Clin. Path. 14: 247–248, 1944.
2. Scherer, J. H., and Howe, J. S.: Fatal cardiac tamponade following sternal puncture, J. Lab. and Clin. Med. 30: 450–453, 1945.
3. Bardham, P. N.: Death from sternal puncture, Indian M. Gaz. 82: 443–508, 1947.

EDITORIAL

PYROGENS

THE term pyrogen was applied by Burdon-Sanderson in 1875 to a hypothetical substance in bacteria-free extracts of putrid meat, which caused fever on injection into animals. Occasional similar observations attracted little attention until Wechselman (1911) showed that the febrile reactions following the administration of solutions of arsphenamine were due to contamination of the distilled water, presumably bacterial. They could be avoided by the use of water sterilized immediately after distillation.

This aroused widespread interest, and it was soon shown that a similar mechanism was involved in the reactions following injection of many other substances, including sodium chloride, glucose, immune sera, citrated blood and proteins of other types. This is now commonplace knowledge, and the chief importance of pyrogens from the purely practical standpoint is still the disturbing reaction which they cause when inadvertently administered. Much of interest has been learned, however, regarding the nature of pyrogens and the details of the reactions, and renewed attempts have been made to utilize these for therapeutic purposes. The subject has been extensively reviewed by Bennett and Beeson.[1]

Although pyrogens may be produced by many varieties of bacteria, Gram-negative bacilli are by far the most potent, particularly the Salmonella, coli-aerogenes and Pseudomonas groups and *Serratia marcescens* (prodigiosus). The chemical nature of pyrogens has not been positively demonstrated, but they are probably not protein as has been widely assumed. Although "purified" bacterial protein is pyrogenic, other proteins such as horse serum and egg white are not, if so handled that bacterial contamination is avoided. There is evidence that pyrogen is a by product of bacterial growth rather than of cellular disintegration.[2] Powerful pyrogens have been prepared from several species of bacteria, which have little or no antigenic activity and which give negative reactions for protein and even for nitrogen. Pyrogen is not destroyed by autoclaving at ordinary temperatures, and it is not removed by filtration through porcelain filters. It does not pass through a collodion membrane, and it can be removed by adsorption on such substances as charcoal or certain ion exchange agents and filtration through a Seitz filter. Pyrogens are believed to be complex polysaccharides of high molecular weight. They are extremely potent, 30 micrograms sufficing to cause a severe reaction in a human subject. They can be demonstrated and titrated by injection into rabbits and dogs.[3]

[1] Bennett, I. L., and Beeson, P. B.: The properties and biological effects of bacterial pyrogens, Medicine 29: 365–400, 1950.
[2] Mondolfo, H., and Hounie, E.: Sobre el origen del pirógeno bacteriano, Día méd. 19: 1724–1725, 1947.
[3] Co Tui and Schrift, M. H.: A tentative test for pyrogens in infusion fluids, Proc. Soc. Exper. Biol. and Med. 49: 320–323, 1942.

The clinical manifestations of the reaction are too well known to merit description. The usual interval of 45 to 90 minutes before the initial rise in temperature suggests that pyrogens act indirectly, probably by causing some tissue injury. Immediately after the injection there is a severe leukopenia, evident within five minutes and followed in an hour or two by a neutrophilic leukocytosis accompanied by a reduction in the absolute number of lymphocytes and eosinophiles. It has been suggested that the latter changes are due to stimulation of the pituitary-adrenal cortex by the stress of the reaction. With defervescence there is a fall in arterial pressure, more marked in hypertensive subjects and sometimes of considerable duration, accompanied by an increase in renal blood blow [4] and cardiac output [5] and a diminution in peripheral resistance.[6] There is also a depression of gastric motility and secretion.

The administration of adequate doses of aminopyrine will diminish or prevent the elevation of temperature and much of the subjective discomfort, but it does not alter the other features of the reaction nor prevent the development of tolerance. Cortisone or ACTH, if administered before the injection, lessens the severity of the reaction and reduces the mortality in animals, especially if adrenalectomized. The effect, if any, is much less definite when these are given at the height of the reaction.

One injection of pyrogen in man or animals results in an increased tolerance which is evident within 24 hours and can be increased by successive injections at one or two day intervals. To duplicate the febrile response the dose on successive injections must be increased two to five fold. Tolerance is not specific but extends to pyrogens from any source. Tolerance is not associated with immunity of the ordinary type, it does not depend upon antibodies and can not be transferred passively to other animals. It diminishes rapidly when injections are stopped, even though specific antibodies are increasing, and it is usually lost after about three weeks. The mechanism of this tolerance is not definitely known, but Beeson [7] has shown that pyrogen disappears from the blood of a tolerant animal more rapidly than from a normal animal and that tolerance can be abolished by intravenous injections of thorotrast or trypan blue which cause blockade of the reticuloendothelial system.

It is not to be inferred that pyrogens, in the restricted sense in which the term has been used, are the only substances which can cause fever, and there is no proof that they are the cause of the fever in ordinary infections. Failure to consider and avoid them, however, has led to many gross errors

[4] Chasis, H., Goldring, W., and Smith, H. W.: Reduction of blood pressure associated with the pyrogenic reaction in hypertensive subjects, J. Clin. Investigation 21: 369–376, 1942.
[5] Grollman, A.: Variations in the cardiac output of man. V. The cardiac output of man during the malaise and pyrexia following the injection of typhoid vaccine, J. Clin. Investigation 8: 25–32, 1929.
[6] Bradley, S. E., et al.: Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction, J. Clin. Investigation 24: 749–758, 1945.
[7] Beeson, P. B.: Tolerance to bacterial pyrogens. II. Rôle of the reticulo-endothelial system, J. Exper. Med. 86: 39–44, 1947.

of interpretation in experiments designed to show the effect of various substances, especially tissue extracts, on the temperature, blood pressure or leukocyte count. Pyrogens derived from contaminating bacteria are probably the cause of "cotton fever" observed in industrial workers who inhale dust from low grades of cotton. It has also been suggested on clinical grounds that pyrogens derived from bacteria in the respiratory passages are the cause of fever seen in workers who inhale the fumes (oxides) of zinc and other metals.

The enthusiastic use of typhoid vaccine and other pyrogens in the treatment of infections, widespread for a while during the second decade of this century, was largely abandoned when it was found that they worked no miracle. There can be little doubt, however, that this form of "fever therapy" may exert a favorable effect on the course of certain infections in some subjects, presumably by a nonspecific stimulation of some of the defensive mechanisms. This is most evident in such diseases as uveitis and other ocular infections in which the severity of the inflammation and the effect of the treatment can be observed directly. It might well be used more frequently than it is in certain other types of infection in which no specific therapy is available and which are resistant to less drastic procedures. Individual variation in susceptibility to pyrogen and in the development of tolerance, however, necessitates considerable experience and agility in adjusting doses so as to get successive reactions of the desired severity. This difficulty, the marked subjective discomfort and the risk in unintentionally violent reactions, particularly in inexperienced hands, are serious practical handicaps.

The induction of a severe pyrogenic reaction in animals causes cellular necroses, particularly in the adrenals but also in the liver, kidney, bone marrow, myocardium and gastrointestinal mucosa. Pyrogens will also excite the Schwartzman reaction, an inflammatory reaction with purpura in areas of the skin which have been prepared by intradermal inoculations of the material a few hours previously. Gratia and Linz (1931) found that injection of pyrogenic bacterial filtrates caused hemorrhage and necrosis in sarcomatous tumors of guinea pigs without a preliminary injection. This led to experiments in human subjects with advanced inoperable malignant neoplasms, in which there was most often employed a highly purified polysaccharide prepared by Shear et al. from *Serratia marcescens*. Holloman[8] and Oakey[9] have each reported observations in a few patients who were given a series of injections. These were followed by a severe febrile reaction with a marked fall in blood pressure, often to a state of shock which was not easily controlled, although all subjects survived. There was usually

[8] Holloman, A. L.: Reactions of patients and of tumors to injections of *Serratia marcescens* polysaccharide in eight cases of malignant disease, Approaches to tumor therapy, Am. Assoc. Advancement Sc. 1947, 273–276.

[9] Oakey, R.: Reactions of patients to injection of *Serratia marcescens* polysaccharide in nine further cases of malignant disease, Approaches to tumor therapy, Am. Assoc. Advancement Sc. 1947, 277–278.

pain in the tumor with transient swelling accompanied by hemorrhage and necrosis (biopsy). In some subjects, including one case of Hodgkin's disease, there was subsequently a reduction in size of the tumor, relief of edema and temporary amelioration of symptoms. The violence of the reactions described seems almost prohibitive, but further controlled study is indicated. Experience with other pyrogens suggests that much of the fever and malaise might be avoided by using antipyretics without materially interfering with the action on the tissues, but the vasomotor reactions may be more difficult to control.

Attempts have also been made to utilize pyrogens in the treatment of hypertension. Chasis et al.[4] in a small series of cases obtained a substantial fall in blood pressure which was maintained during a series of injections lasting up to a month and throughout a subsequent period of observation of 12 days. Aminopyrine did not interfere with this response. The effect was attributed to an "adverse or asthenic action on the cardiovascular system" rather than on the underlying cause of the hypertension.

Page and Taylor[10] studied the effect of protracted treatment with a purified bacterial pyrogen in a series of cases of malignant hypertension. Of 14 patients who did not stop the treatment prematurely, in 11 with good renal function there was a "reversal" of the "malignant" features, with a fall in blood pressure. After an interval of from two to six months there was a gradual rise in blood pressure in most of them, but relapse occurred in only one. They later reported[11] that eight of the 11 patients were living, with an average time of survival of 32 months, and they were leading useful lives without evidence of progressive renal insufficiency. Patients with renal insufficiency did not respond well.

This form of treatment is also still in the early experimental stage, and in its present form it is manifestly a drastic and cumbersome procedure. It seems possible, however, that it might be so modified as to be feasible in selected cases of this serious disease.

<div align="right">P. W. C.</div>

[10] Page, I. H., and Taylor, R. D.: Pyrogens in the treatment of malignant hypertension, Mod. Concepts Cardiovas. Dis. 18: 51–52, 1947.
[11] Taylor, R. D., Corcoran, A. C., and Page, I. H.: Further experience with bacterial pyrogens in the treatment of malignant hypertension, J. Lab. and Clin. Med. 34: 1756–1757, 1949.

REVIEWS

Medical Entomology, with Special Reference to the Health and Well-Being of Man and Animals. 4th Ed. By WILLIAM B. HERMS, Sc.D. 643 pages; 15.5 × 24.5 cm. The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 1950. Price, $9.00.

This is the fourth edition of a book, originally entitled *Medical and Veterinary Entomology*, which appeared 35 years ago. It was based on courses conducted by its author at the University of California for some six years. At that time, medical entomology was an infant among the applied biological sciences. To its growth and development during the ensuing years Professor Herms contributed mightily by his research and teaching, and by bringing together periodically the scattered but extensive and increasing literature concerning insects and other arthropods of medical importance. The new volume will be his final personal contribution for he died on May 9, 1949, the day after he had completed the typescript of this book.

The present edition is a complete revision of the previous texts but adheres to the same general plan of presentation. An excellent chapter on the history of medical entomology is followed by instructive comments on the nature, scope, and methodology of this specialty, on parasites and parasitism, and how arthropods cause and carry disease. The next section is expository, dealing with their structure, development, classification, and means of identification. The rest of the book—some 85 per cent of the total pages—takes up group by group the different kinds of insects and arachnids of medical significance, discussing their nomenclature, recognition, the disorders they cause or convey with occasional notes on the treatment of these illnesses, and lastly methods of control. This last is dealt with exhaustively. Lists of selected references follow each chapter.

In addition to the solid core of descriptive medical entomology which enlarged with each revision, the fourth edition is enriched by its content concerning war-connected discoveries and developments in this field. Thus there are frequent allusions to the rôles of modern insecticides and repellents in preventing military and post-war malaria; louse-, flea-, and mite-borne typhus; dengue fever; sand-fly fever; filariasis; fly-transmitted enteric infections; etc. The author stresses his conviction, however, that "shot-gun" methods of applying these chemicals have been too prevalent with adverse effect upon certain balances in nature. He believes that more fundamental knowledge of the life-history of disease vectors and of the ecology both of the transmitting organisms and of their faunal associates is essential to the wise and successful use of the new insecticides.

There are few faults of omission or commission to depreciate the superior quality of this work. It was noted in certain instances that page references in the Index were more proximate than exact. The special precautions widely advocated regarding the use of halogenated hydrocarbon insecticides in dairy barns and on cattle are not mentioned. The same is true of the classic demonstration by Watt and Lindsay in Texas of the importance of fly control in preventing shigellosis. This latter work merits inclusion in the chapter on the history of medical entomology. The subject of resistance of insects to chemical insecticides should have received more attention.

The book is bountifully and well illustrated. Its style shows the effect of years of successful teaching; it will engage and stimulate the interest of anyone with an inquiring mind. Technically, it will probably be more useful to the public health entomologist than to practicing physicians, due to its emphasis on control and prevention rather than treatment. In this connection, however, it should be noted that the final chapter, "Venomous and Urticarial Arthropods," will be of special interest to

the medical man.   Professor Herms' last work is and will remain for a long time to come an authoritative source of information about insects and arachnids of medical and public health importance.

JUSTIN M. ANDREWS

The Normal Encephalogram.   4th Ed.   By LEO M. DAVIDOFF, M.D., and CORNELIUS G. DYKE, M.D.   240 pages; 15.5 × 24 cm.   Lea and Febiger, Philadelphia.   1951. Price, $6.00.

This third edition is similar to the second except for minor corrections.   The outline of the chapters is practically the same as in the second edition.   The first chapter deals with general considerations including a brief historical sketch, then indications and contraindications, technic of encephalography including the roentgen technic. The reactions to encephalography and mortality are also discussed in a clear and complete manner.   This first chapter is concise, well illustrated and lucid.   It answers all the questions one would like to know in general about encephalography.

The second chapter deals with definite constructive intracranial structures.   In this chapter the normal appearance of the ventricles, aqueduct of Sylvius and intraventricular foramen, both in the contrast air studies and actual brain sections, is discussed.   The anatomy of these systems is well delineated together with a good review of the literature on the various parts.

The third chapter deals with the external portions of the brain, convolutions, and sulci.   It is amazing, but supported by very good air plates, how many of the convolutions and sulci can actually be visualized by air.   The photography in this chapter is excellent.

The fourth chapter deals with the subarachnoid systems and their sulci.   The anatomy is discussed and accompanied by well illustrated plates together with the corresponding air plate which form a fine collection.

Chapter 5 deals with the intracranial structures and their related fluid spaces such as corpus callosum, thalami caudate nuclei, septum pellucidum, fornix, anterior and posterior commissures, intermediate mass, cerebellum and choroid plexus.   In fact, any of the parts of the brain that can be located anatomically, has been illustrated by air plates in this chapter.   It is an excellent and instructive compilation which is of great value.   Even the cerebral arteries are visualized by air.

To sum up briefly, this edition offers an excellent descriptive, comparative, and visual means of studying the living brain by encephalography.   It is of inestimable value, not only to the neurosurgeon but also to the neuroanatomist, for it is really the neuroanatomy of the living brain.   It gives definite and accurate basis for a base line as far as normal structure of the living brain is concerned.   When one completes the study of this edition, there is very little, if any, more information concerning this subject to be gleaned from any other source.   This book should be a Bible for every roentgenologist and neurosurgeon and anybody who expects to interpret intelligently the conditions affecting the central nervous system.

L. M.

Calcific Disease of the Aortic Valve.   By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, and SIMON KOLETSKY, M.D., of the Institute of Pathology, Western Reserve University and the University Hospitals of Cleveland.   111 pages; 15.5 × 23.5 cm.   J. B. Lippincott Company, Philadelphia. 1947.   Price, $5.00.

This monograph is a detailed survey of the literature on this subject, and a comprehensive report and statistical analysis of 200 autopsied cases, including clinical and

pathological findings. The material is clearly presented, and serves as a basis for the authors' conclusion that, "with only rare exceptions, calcific disease of the aortic valve is the result of rheumatic cardiac disease." This small volume should be of interest to both pathologists and cardiologists.

S. S.

Therapeutics in Internal Medicine. Edited by FRANKLIN A. KYSER, M.D., M.S., F.A.C.P. 715 pages; 17 × 25 cm. Thomas Nelson and Sons, New York. 1950. Price, $12.00.

This new volume of therapeutics has been written by 81 contributors who comprise, in the editor's words, "a group of outstanding men whose investigations and teaching experience in certain phases of internal medicine qualify them to make authoritative statements."

The text is basically limited to therapy; but in certain sections, where they seem necessary for an intelligent approach to treatment, physiological principles, clinical descriptions and classifications, and etiological factors, have been briefly presented in helpful introductory paragraphs. A total of about 270 sections covers the whole range of internal medical diseases. Chapters on common dermatological and neurological problems are included.

This book makes its debut at the close of medicine's most sensational therapeutic decade. The pace of discovery and application has so accelerated that editing a text of this kind is a stupendous task; to have every topic comparably up-to-date is well nigh impossible, and there are consequent discrepancies. For example, there is a hastily appended section, overlong and overfull, on Terramycin, with more than thirty (mostly unpublished) 1950 references. In contrast, the section dealing with pernicious anemia was apparently written in 1948 and includes therefore none but the earliest experiences with vitamin B_{12}. In fact at one point the vitamin is relegated in these terms, "If sensitivity becomes a serious problem, 30 mg. (*sic*) of Vitamin B_{12} may be substituted for each 15 units of liver extract."

Despite a few such deficiencies, the text as a whole maintains an exceptionally high standard. It is written for the most part in a highly practical way, so that the reader will have little difficulty in carrying out the writer's suggestions. There are, however, exceptions to this generalization. Thus the treatment of amebic dysentery is dealt with in such a way that the reader cannot be sure just what is recommended.

Other minor defects include one or two instances of "verbicide," such as "pruritis" and "decubiti"—uncomfortable bedfellows; and it is hard to see the value of such statistical summaries as "sixty per cent of all cases [of erysipelas] occur between the ages of 30 and 70." Some readers may justifiably be startled at the permission granted on p. 513 to give up to 2.4 mg. of strophanthin within eight hours.

Every practitioner, whether he likes it or not, is frequently compelled to treat symptoms *per se*, and the book therefore might well be enhanced by a section on important symptomatic treatment.

Between its garish silver covers, this volume contains a treasury of easily assimilated information. Readability is favored by two-column printing on non-shiny paper. All in all the text can be well recommended to internists and general practitioners, and also to students—who so frequently complain that they glean too little of practical therapy in the fourth year.

H. J. L. M.

When Minds Go Wrong: A Simple Story of the Mentally Ill—Past, Present and Future. By JOHN MAURICE GRIMES, M.D. 237 pages; 15.5 × 23.5 cm. Published and distributed by the author, 5209 South Harper Avenue, Chicago 15. 1949. Price, $5.00.

The author of this book states that he has spent 20 years in seven different state hospitals in the East, and that he once made an investigation of conditions in state hospitals for the American Medical Association. Although the author states that he has been a psychiatrist for 20 years he is not a member of the American Psychiatric Association, nor has he been certified by the American Board of Psychiatry and Neurology. His book is the culmination of his ideas about the care of the mentally ill and is aimed at revolutionizing the present system of state psychiatric hospitals. His criticisms of the present system are extremely biased, and are not adequately substantiated by facts, although some statistics are given. His answer to these criticisms is to do away with state hospitals altogether and to replace them by villages. His proposed methods of achieving this idealistic solution are not sound. This book has been published privately, and is being distributed to doctors at the expense of the author. The general subject of the book is one which needs consideration, but this book does not treat the subject adequately.

H. W. N.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas of Histologic Diagnosis in Surgical Pathology. By KARL T. NEUBUERGER, M.D., Professor of Pathology, University of Colorado School of Medicine, Denver, Colorado; with a Section on Exfoliative Cytology by WALTER T. WIKLE, B.S., M.S., M.D., Assistant Professor of Pathology, University of Colorado School of Medicine, Denver, Colorado; Photography by GLENN E. MILLS, B.A., M.A., Department of Visual Education, University of Colorado School of Medicine, Denver, Colorado. 460 pages; 26 × 18 cm. 1951. The Williams & Wilkins Company, Baltimore. Price, $11.00.

Biological Antioxidants: Transactions of the Fourth Conference, December 8–9, 1949, New York, N. Y. Edited by COSMO G. MACKENZIE, Department of Biochemistry, University of Colorado School of Medicine; Associate Editors: E. V. JENSEN, Departments of Surgery and Chemistry, University of Chicago School of Medicine, and RALPH T. HOLMAN, Department of Biochemistry and Nutrition, Agricultural and Mechanical College of Texas. 181 pages; 23.5 × 15.5 cm. (paperbound). 1950. Josiah Macy, Jr. Foundation, New York. Price, $3.25.

Blood Clotting and Allied Problems: Transactions of the Third Conference, January 23–24, 1950, New York, N. Y. Edited by JOSEPH E. FLYNN, Department of Pathology, College of Physicians and Surgeons, Columbia University. 224 pages; 23.5 × 15.5 cm. 1950. Josiah Macy, Jr. Foundation, New York. Price, $3.00.

Faith Healing and Healing Methods Founded Thereon, Including Dr. Shipsey's Healing Methods Scientifically Explained; Its Relationship to Christian-Science, Spiritualism and Prayer; etc.; Scientific reasons why all people should pray to God to heal their illnesses and get stronger. By DR. MICHAEL SHIPSEY, M.B., B.Ch.,

Royal University of Ireland. 123 pages; 18.5 × 12.5 cm. 1950. Printed at the Press of A. H. Saxton (Printers) Ltd., Birmingham, England; copyright 1950 by Michael Shipsey. Price, 10/6.

Family Centered Maternity and Infant Care: Report of the Committee on Rooming-In of the Josiah Macy, Jr. Foundation Conference on Problems of Infancy and Early Childhood. Edited by EDITH B. JACKSON, M.D., Departments of Pediatrics and Psychiatry, Yale University School of Medicine, New Haven, Connecticut, and GENEVIEVE TRAINHAM, R.N., M.A., Director, Infant Growth Laboratory, Merrill-Palmer School, Detroit, Michigan; with the Assistance of Members of THE ROOMING-IN COMMITTEE. 29 pages; 23 × 15 cm. (paper-bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, 1–25 copies, 25¢ each; 26–100 copies, 15¢ each; 101 copies or more, 10¢ each.

Fundamentals of Clinical Fluoroscopy, with Essentials of Roentgen Interpretation. By CHARLES B. STORCH, M.D., Adjunct, Radiodiagnostic Department and Radiotherapy Department, Beth-El Hospital, Brooklyn, New York. 196 pages; 26 × 18 cm. 1951. Grune & Stratton, Inc., New York. Price, $6.75.

A Guide to Medicine. By Ivo GEIKIE-COBB, M.D.; with Special Articles by Various Contributors. 416 pages; 23 × 15 cm. 1951. Duell, Sloan and Pearce, New York. Price, $5.00.

The Low Fat, Low Cholesterol Diet: What to Eat and How to Prepare It. By E. VIRGINIA DOBBIN, Senior Dietitian, E. V. Cowell Memorial Hospital, University of California, Berkeley; HELEN F. GOFMAN, M.D., San Francisco; HELEN C. JONES, Home Economist, Berkeley; LENORE LYON, San Jose, and CLARA-BETH YOUNG, Dietitian, E. V. Cowell Memorial Hospital, University of California, Berkeley; Introduction by THOMAS P. LYON, M.D., Research Associate in Medical Physics, Donner Laboratory, University of California, Berkeley, etc.; and JOHN W. GOFMAN, Ph.D., M.D., Associate Professor Medical Physics, Donner Laboratory, University of California, Berkeley, etc. 371 pages; 22 × 14 cm. 1951. Doubleday & Company, Inc., Garden City, New York. Price, $3.45.

Metabolic Interrelations: Transactions of the Second Conference, New York, N. Y., January 9–10, 1950. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York, N. Y.; Editorial Assistant: VIVIAN JOHNSON. 279 pages; 23 × 15.5 cm. (paper-bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, $3.95.

The Normal Encephalogram. Ed. 3. By LEO M. DAVIDOFF, M.D., Director of Neurological Surgery, Beth Israel Hospital, New York City, etc.; and CORNELIUS G. DYKE, M.D., Late Associate Professor of Radiology in the College of Physicians and Surgeons, Columbia University, etc. 240 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $6.00.

Pharmacology. By MICHAEL G. MULINOS, M.D., A.B., A.M., Ph.D., Associate Professor of Physiology and Pharmacology, New York Medical College, Flower and Fifth Avenue Hospitals, New York, New York; with a Foreword by CHARLES C. LIEB, A.B., M.D., Hosack Professor Emeritus of Pharmacology, College of Physicians and Surgeons, Columbia University. 484 pages; 22 × 14.5 cm. 1951. Oxford University Press, New York. Price, $5.00.

Physiology of Shock. By CARL J. WIGGERS, M.D., Sc.D., F.A.C.P., Professor of Physiology and Director, Department of Physiology, School of Medicine, Western Reserve University. 459 pages; 24 × 16 cm. 1950. The Commonwealth Fund, New York. Price, $5.00.

Serum Sickness. By C. FRH. VON PIRQUET, M.D., and BELA SCHICK, M.D.; translated by BELA SCHICK, M.D. 130 pages; 23.5 × 15.5 cm. 1951. The Williams and Wilkins Company, Baltimore. Price, $3.50.

Symposium on the Healthy Personality: Transactions of Special Meetings of Conference on Infancy and Childhood, June 8–9 and July 3–4, 1951, New York, N. Y. Supplement II: Problems of Infancy and Childhood: Transactions of Fourth Conference, March, 1950. Edited by MILTON J. E. SENN, M.D., Departments of Pediatrics and Psychiatry, School of Medicine, Yale University. 298 pages; 23.5 × 15.5 cm. 1950. Josiah Macy, Jr. Foundation, New York. Price, $2.50.

COLLEGE NEWS NOTES

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Edgar Schall Henry, Sewickley, Pa.
Dr. Emilie Viett Rundlett, Jersey City, N. J.
Dr. Eugene S. Talbot, Chicago, Ill.
Dr. Herbert E. Christman, Lakewood, Ohio
Dr. Frank P. Goodwin, Jamestown, N. Y.
Dr. Ralph Waldo Mendelson, Albuquerque, N. M.
Dr. William Calvert Chaney, Memphis, Tenn.
Dr. Robert Cooke Kimbrough, Jr., Knoxville, Tenn.
Dr. Sidney Adler, Detroit, Mich.
Dr. Irving I. Edgar, Detroit, Mich.
Dr. George H. Houck, Palo Alto, Calif.
Dr. William H. Smith, Baltimore, Md.
Dr. Robert W. Langley, Los Angeles, Calif.
Dr. John O. Westwater, Los Angeles, Calif.
Dr. Howard M. Sheaff, Oak Park, Ill.
Dr. Edward Randall, Jr., Galveston, Tex.
Dr. George W. Lynch, Boston, Mass.
Dr. J. David Roger, Ottawa, Ont., Canada
Dr. John A. Schindler, Monroe, Wis.
Dr. Maxwell L. Gelfand, New York, N. Y.
Dr. Frank A. Marshall, Weehawken, N. J.

A.C.P. Postgraduate Course in Cardiology Conducted at Philadelphia

From January 22 to 27, 1951, the American College of Physicians conducted one of its most outstanding courses entitled, "Modern Trends in Diagnosis and Treatment of Heart Disease," at its headquarters in Philadelphia under the directorship of Dr. William G. Leaman, Jr., F.A.C.P., and in coöperation with the Woman's Medical College of Pennsylvania and other Philadelphia institutions. The faculty included the outstanding authorities in the field of Cardiology and related subjects, not only in Philadelphia but from the East and Middlewest. While the class was restricted to 100 physicians (coming from twenty-one states, Cuba and Canada), one session, a panel discussion on the Current Trends in the Treatment of Hypertension, was held at the Naval Hospital of Philadelphia and an invitation extended to members of the Philadelphia Heart Association, the Section on General Medicine of the College of Physicians of Philadelphia and to other interested physicians in the area. The panel leaders included Dr. Charles C. Wolferth, F.A.C.P., Professor of Medicine and Administrator of the Robinette Foundation of the University of Pennsylvania School of Medicine, Dr. Joseph H. Hafkenschiel, Instructor in Medicine at the University of Pennsylvania School of Medicine, Dr. Harold A. Zintel, F.A.C.S., Assistant Professor of Surgery in the University of Pennsylvania School of Medicine, and Dr. Richard A. Kern, F.A.C.P., Professor of Medicine at Temple University School of Medicine. Captain Julian Love, (MC), USN, F.A.C.P., Chief of the Medical Service

at the Naval Hospital, was the moderator. Approximately seven hundred physicians were in attendance, and it was one of the signal sessions, not only of this course but of any course the College has conducted. Following the session the Commanding Officer of the Hospital, Rear Admiral Clyde Brunson, entertained on behalf of the Naval Hospital the entire group at a cafeteria supper.

A.C.P. POSTGRADUATE COURSES: WINTER AND SPRING, 1951

No. 1, PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN CARDIOVASCULAR DISEASES: University of Southern California School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director; February 12–17, 1951.

This course has been very successfully concluded for a group of 23.

No. 2, RECENT PROGRESS IN INTERNAL MEDICINE: University of Oregon Medical School, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director; March 19–23, 1951.

This course also has been concluded. The excellence of the course deserved a much larger registration than it had, but a smaller proportion of members in the Far West pursue postgraduate courses than is the case in the Middle West and East.

No. 3, CLINICAL ELECTROCARDIOGRAPHY: Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director; March 26–31, 1951.

Although this is the first time this particular course has been offered by the College, it proved to be one of the most popular courses ever given with a registration of approximately 100 physicians.

No. 4, DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Leo H. Criep, M.D., Director; April 24–28, 1951.

This course is still open for registration. It is one of the best courses ever organized in the field of allergy and allied conditions and will be given under the most favorable conditions and with superior accommodations.

No. 5, SOME RECENT DEVELOPMENTS IN THE PRINCIPLES AND PRACTICE OF MODERN INTERNAL MEDICINE: Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director; May 7–11, 1951.

Registration is still open. A superior course, planned as part of the 200th Anniversary Commemorative Exercises of the Pennsylvania Hospital. Prospects indicate registration to a maximum of 100.

No. 6, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D., Director; May 14–19, 1951.

This popular course is already oversubscribed and no further applications for the current year can be accepted.

No. 7, DYNAMIC THERAPEUTICS OF CHRONIC DISEASES: New York University-Bellevue Medical Center, Institute of Physical Medicine and Rehabilitation, New York, N. Y.; Howard A. Rusk, M.D., F.A.C.P., Director; May 21–25, 1951.

Registration still open. The purpose of this course is the presentation of recently evolved dynamics regarding the total rehabilitation of patients with chronic disabling disease. It will be a distinctly superior course and appears for the first time on the College schedule.

No. 8, INTERNAL MEDICINE: Boston University School of Medicine, Massachusetts Memorial Hospitals, Boston, Mass.; Chester S. Keefer, M.D., F.A.C.P., Director; June 4–8, 1951.

Registration still open. This course is given during the week preceding the Annual Session of the American Medical Association at Atlantic City, thus affording an opportunity for physicians from more distant points to both take this course and attend the A. M. A. Session. The course will be conducted on the symposium plan and the various divisions include infectious diseases, heart disease and hypertension, endocrine disorders, thoracic tumors and infections, anemia and lymphoma, gastrointestinal diseases, peripheral vascular diseases, thrombo-embolic disease, and cancer. A superior faculty and the most favorable season for a week's stay in Boston.

For course outlines and registration forms, address the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

ELECTIONS TO MEMBERSHIP, AMERICAN COLLEGE OF PHYSICIANS

The following elections to membership by the Board of Regents took place November 12, 1950, but inadvertently were not published in the December, 1950, issue of this journal.

The next meeting of the Board at which further elections will take place will be at the St. Louis Annual Session, April 8, 1951. Proposals must be filed in the Executive Offices of the College at least sixty days in advance of action; thus any proposals filed after February 9, 1951, will be carried over to the autumn (November, 1951) meeting of the Board of Regents.

(*FELLOWS, FULL CAPITALS*: *Associates, lower case*)

Arthur Simon Abramson..........................White Plains, N. Y. (V.A.)
Daniel K. Adler.................................Syracuse, N. Y.
Sinclair Tousey Allen, Jr.......................Burlington, Vt.
John William Allgood............................Greensboro, N. C.
CHARLES EDWARD ANDERSON, JR.......Shreveport, La.
DAVID IRVING ARBUSE....................New York, N. Y.
JOHN JOSEPH ARCHINARD................New Orleans, La.
SINCLAIR HOWARD ARMSTRONG, JR......Chicago, Ill.
DONALD HERMAN ATLAS.................Highland Park, Ill.

E(dward) Reid Bahnson.........................Winston-Salem, N. C.
ARTHUR DWIGHT BALDWIN..............Wellesley, Mass.
Harry Edgar Banghart...........................Philadelphia, Pa.
GLENN LEWIS BARNUM....................Pasadena, Calif.
Jeanne Cecile Bateman..........................Washington, D. C.
Robert Gordon Baxter...........................Montreal, Que., Can.
Evart Malcolm Beck............................Indianapolis, Ind.
RICHARD TOWNSEND BEEBE.............Loudonville, N. Y.
John Latham Bell...............................Honolulu, T. H.
Martin S. Belle................................Miami, Fla.
Hugh deE. Bennett..............................Chicago, Ill. (V.A.)

Morris Berk.....................................Piedmont, Calif. (V.A.)
Herman Bernhardt............................Montgomery, Ala. (V.A.)
LESTER SYLVAN BLUMENTHAL..........Washington, D. C.
James Francis Blute, Jr.........................Fall River, Mass.
EDWARD LEWIS BOSWORTH, JR..........Rome, Ga.
Thomas Harry Bottomley, Jr...................Port Huron, Mich.
Joseph Peter Brady............................Flushing, N. Y.
George Joseph Brebis..........................Glenview, Ill.
ROBERT JACOB BROTCHNER..............St. Paul, Minn.
Laurence Wilmott Brown......................Ottawa, Ont., Can.
Francis Ernest Bruno..........................Hartford, Conn.
MARTIN STOWELL BUEHLER............Dallas, Tex.
JAMES OTEY BURKE........................Richmond, Va.
Norman Burnstein.............................Jackson, Miss. (V.A.)
WILLIAM COOPER BUSCHEMEYER........Louisville, Ky.

Douglas George Cameron......................Montreal, Que., Can.
Charles Sumner Campbell......................Salem, Ore.
Vito Francis Cangemi.........................Jersey City, N. J.
MARGIL CLINTON CARLISLE..............Waco, Tex.
FRANCIS BRIAN CARROLL.................Waban, Mass. (V.A.)
Irvin Norwood Carroll.........................Christiana, Del. (V.A.)
Jesse Frank Casey..............................Topeka, Kans. (V.A.)
Isaac Benjamin Cippes.........................Miami, Fla.
DONALD FRANKS CLOSTERMAN..........Kingston, Pa.
George Charles Coe............................Chicago, Ill.
Walter Slater Coe..............................Louisville, Ky.
Robert Archibald Coen.........................Portland, Ore.
WILLIAM BERNARD COEN.................Springfield, Mass.
John Hooper Coffey............................Amarillo, Tex. (V.A.)
William Leo Coffey, Jr........................Milwaukee, Wis.
MICHAEL AARON COGAN.................Springfield, Mass.
Irvin Joseph Cohen............................New York, N. Y. (V.A.)
Jerome Louis Cohen............................Troy, N. Y.
Egidio Sadot Colón-Rivera.....................Santurce, P. R.
MERL GREENE COLVIN.....................Williamsport, Pa.
Ellison Richard Cook, III......................Savannah, Ga.
J(OSEPH) RUSSELL COOK.................Huntington, W. Va.
Herbert William Coone.........................M. C., U. S. Air Force
TALBERT COOPER...........................Rochester, Minn.
HOWARD LEROY CORRELL................Milwaukee, Wis.
Warren Coons Corwin..........................Fayetteville, Ark. (V.A.)
RICHARD SHERIDAN COSBY...............San Marino, Calif.
Nicholas John Cotsonas, Jr.....................Washington, D. C.
Jerome Arthur Covey...........................Great Neck, N. Y.
David Mark Craig..............................St. Paul, Minn.
JOSEPH HAMILTON CRAMPTON..........Seattle, Wash.
Kenneth Adams Crockett.......................Salt Lake City, Utah
Walter Shelley Culpepper......................New Orleans, La.

SIDNEY DAVIDSON...........................Lake Worth, Fla.
John Howard Davis.............................Beverly Hills, Calif.
Harold Everhard DePree........................Kalamazoo, Mich.

Warren Henry Diessner..........................M. C., U. S. Army
Sim Pope Dimitroff..............................Los Angeles, Calif.
ALEXANDER ANDREW DOERNER.........U. S. Public Health Service
Albert Herbert Domm............................Los Angeles, Calif.
Alfred Stanley Dooneief.........................Bedford Hills, N. Y.
Wilfred Dorfman................................Brooklyn, N. Y.
Virgil Jackson Dorset...........................U. S. Public Health Service
Gilbert Franklin Douglas, Jr.....................Birmingham, Ala.
Charles Frederick Downing.......................Decatur, Ill.
Daniel Francis Downing..........................Philadelphia, Pa.

A(lfred) Chesmore Eastlake, Jr..................New York, N. Y.
HENRY DUNLOP ECKER...................Washington, D. C.
Kleberg Eckhardt................................Corpus Christi, Tex.
SIDNEY EDWIN EISENBERG...............New Britain, Conn.
STEPHEN REGINALD ELEK................Los Angeles, Calif.
Daniel Sumner Ellis.............................Brookline, Mass.
DAVID EDWIN ENGLE.....................Tucson, Ariz.
Edward Robert Evans............................Pasadena, Calif.
John Radcliffe Ewan.............................Washington, D. C.
John Dunham Eyre, Jr...........................Manchester, N. H. (V.A.)

Robert Francis Farrington.......................Miami, Fla.
Seymour Leonard Felder..........................New York, N. Y.
JOHN BUCKLEY FERSHTAND..............Fort Worth, Tex.
John Francis Filippone..........................Albany, N. Y.
Herman Finkelstein..............................Williamsport, Pa.
Edison David Fisher.............................Los Angeles, Calif.
George Seibert Fisher...........................Detroit, Mich.
Hyman Louis Fittingoff..........................Philadelphia, Pa.
FREDERICK WILLIAM FITZ.................Chicago, Ill.
Herbert Eldridge Flewelling.....................Jaffrey, N. H.
Martin Eugene Flipse............................Miami, Fla.
MARK ANTHONY FOSTER..................Madison, Wis.
Noble Owen Fowler, Jr..........................Cincinnati, Ohio
Nathan Frederick Fradkin........................Albany, N. Y.
JOSEPH JEROME FRANKEL...............Wilkes-Barre, Pa. (V.A.)
Bernard Irving Freedman.........................New York, N. Y.
Leo David Freydberg............................Troy, N. Y.
GERALD JONAS FRIEDMAN.................New York, N. Y.
H(enry) Harold Friedman.........................Denver, Colo.
ROBERT HOWARD FURMAN...............Nashville, Tenn.

James Jackson Gable, Jr.........................Oklahoma City, Okla.
WILLIAM DUDLEY GAMBILL.............Indianapolis, Ind.
Henry Gann.....................................White Plains, N. Y.
BENJAMIN MORRIS GASUL.................Chicago, Ill.
Isadore Earle Gerber............................New York, N. Y.
FREDERICK GEORGE GILLICK.............U. S. Public Health Service
Alfred Francis Goggio...........................Berkeley, Calif.
MILTON JOSEPH GOLDSTEIN.............Scranton, Pa.
Milton Wilbert Golomb..........................Pittsburgh, Pa.
Seaburt Goodman................................Birmingham, Ala.

William Emerson Goodpastor....................New Castle, Pa.
ABRAHAM GOOTNICK.......................Brooklyn, N. Y. (V.A.)
Harold Gorenberg................................Jersey City, N. J.
David Lloyd Graller............................Cincinnati, Ohio
ARTHUR MORTON GREENE...............Omaha, Nebr.
Regina Stolz Greenebaum........................Kerrville, Tex. (V.A.)
HERBERT GREENFIELD....................Newark, N. J.
Arthur Herman Griep............................Evansville, Ind.
Robert Leland Griffith..........................U. S. Public Health Service
Robert Leslie Grissom...........................River Forest, Ill.
Christian Gronbeck, Jr...........................M. C., U. S. Army
Ludwik Gross...................................New York, N. Y. (V.A.)
Seymour Gruber.................................Brooklyn, N. Y.
Vernon Gage Guenther...........................Oshkosh, Wis.
Silvio Mario Guglielmelli........................Brooklyn, N. Y.
Leonard Beryl Gutner...........................White Plains, N. Y.

William Reid Haas...............................M. C., U. S. Army
*Thomas Arthur Haedicke........................Washington, D. C.
RUSSELL BRATTON HANFORD............Spokane, Wash.
Harold Abraham Hanno..........................Philadelphia, Pa.
Bernard Lauriston Hardin, Jr....................Washington, D. C.
RICHARD LAMAR HARRIS.................Peekskill, N. Y. (V.A.)
Glen Webber Harvey, Jr.........................Cedar Rapids, Iowa
LOUIS PEASE HASTINGS....................Hartford, Conn.
Harvey Allan Hatch.............................Idaho Falls, Idaho
DON VIRGIL HATTON.......................Oak Hill, W. Va.
WILLIAM EDWIN HAY.....................Denver, Colo.
William Derrel Hazlehurst.......................Macon, Ga.
Elmer Wesley Heffernon.........................Watertown, Mass.
Victor Oscar Hertzman..........................Vancouver, B. C., Can.
George Alfred Hess..............................Titusville, N. J.
Robert Wright Hillman..........................Brooklyn, N. Y.
Ralph Gorman Hills.............................Baltimore, Md.
James Harvey Bruce Hilton......................Ottawa, Ont., Can.
Gerhard Rudi Hirschfeld.........................Lyons, N. J. (V.A.)
THOMAS GIDEON HOBBS...................Lexington, Ky.
ELLIOT HOCHSTEIN..........................New York, N. Y.
HOWARD LAMAR HOLLEY..................Birmingham, Ala.
JOSEPH HENRY HOLMES...................Denver, Colo.
Howard Lowell Horns............................Minneapolis, Minn.
JOHN CAMPBELL HORTENSTINE.........Winchester, Va.
Tyron Ehrhart Huber............................M. C., U. S. Army
RALPH HENRY HUFF.......................Tacoma, Wash.
Joan Humphrey-Long............................Philadelphia, Pa.
SAMUEL HURWITZ..........................Jamestown, N. Y.
John Henry Huss................................Meriden, Conn.

EDWIN NEWTON IRONS...................Chicago, Ill.

JAMES S. L. JACOBS.........................Long Beach, Calif. (V.A.)
Abraham Solomon Jacobson.......................New York, N. Y. (V.A.)

 * (MC), AUS.

Sydney Jampel...................................Yonkers, N. Y. (V.A.)
James Garfield Janney, Jr.......................University City, Mo.
Emil Jobb.......................................Seattle, Wash.
Donald Lee John................................Burbank, Calif.
C(HESTER) EARLE JOHNSON, JR..........Staunton, Va.
JOHN BEAUREGARD JOHNSON............Washington, D. C.
Joseph Edward Josephson........................St. John's, Newfoundland, Can.

Bernard I. Kahn...............................M. C., U. S. Navy
SIDNEY RICHARD KALISKI................San Antonio, Tex.
William Kaufman...............................Bridgeport, Conn.
William Richard Kay............................Richmond, Va.
JOHN WESLEY KEYES......................Detroit, Mich.
NEWTON ALVIN KILGORE, JR.............Houston, Tex.
LESLIE GEORGE KINDSCHI................Monroe, Wis.
John Weaver King..............................Cleveland, Ohio
ROBERT CHENAULT KINGSLAND.........Clayton, Mo.
MARTIN MARCEL KIRSHEN................Chicago, Ill.
Charles E. Klontz..............................Rockford, Ill.
Henry Roebling Knoch.........................Philadelphia, Pa.
Robert Eugene Koch............................St. Louis, Mo.
Maxwell Howard Kolodny......................Yonkers, N. Y. (V.A.)
Herbert Koteen.................................New York, N. Y.
Stanford Shea Kroopf..........................Palo Alto, Calif.
Sam Kruger.....................................Chicago, Ill. (V.A.)

John Raymond Laadt...........................Chicago, Ill.
Ralegh Howard Lackay.........................M. C., U. S. Air Force
FRANK LAMBERTA...........................Jamaica, N. Y.
Emanuel Peter LaMotta........................New York, N. Y.
Edward Everett Landis.........................Anchorage, Ky.
Francis Bertold Landis.........................Milwaukee, Wis. (V.A.)
VALORUS FREDERICK LANG.............Milwaukee, Wis.
ALBERT WEINFIELD LAPIN...............Montreal, Que., Can.
Charles Harris Lawrence........................Chicago, Ill.
H(enry) Sherwood Lawrence...................New York, N. Y.
Robert Clyde Lawson...........................Oklahoma City, Okla.
William Arthur Leff............................Newark, N. J.
James Liebmann Leland........................New York, N. Y.
JULIAN PAUL LEVINSON...................Pittsburgh, Pa.
IRVING MILTON LEVITAS..................Westwood, N. J.
JOSEPH LEVY.................................New Rochelle, N. Y.
ABRAHAM LIEBERSON.......................New York, N. Y.
Karl Anthony Liefert...........................Wauwatosa, Wis.
A. EDWARD LIVINGSTON..................Bloomington, Ill.
Arthur John Lockhart..........................Boston, Mass.

Frank Goodnow MacMurray...................Washington, D. C.
William Paul Maddux...........................Springfield, Mo.
Connolly James Malloy.........................Montreal, Que., Can.
John Joseph Manning...........................Park Ridge, Ill. (V.A.)
JAMES SCOTT MANSFIELD.................Brookline, Mass.
Harold Margulies..............................Des Moines, Iowa

FRANK ANTON MARSHALL................Weehawken, N. J.
Edward Martin..................................New Britain, Conn.
Howard Leslie Mawdsley......................San Mateo, Calif.
Russell Milton Maynard.........................M. C., U. S. Navy
STEVEN ANTHONY MAZAR...............Binghamton, N. Y.
Janet Ward McArthur...........................Boston, Mass.
THOMAS CROOKE McCLEAVE, JR..........Oakland, Calif.
James Grant McFetridge........................Regina, Sask., Can.
HAROLD HIQUES McLEMORE.............Spokane, Wash.
JOSEPH WILLIAM McMEANS, Jr...........Florence, S. C.
Jerome Saul Mehlman..........................Chicago, Ill.
Leonard Edward Meiselas.....................Brooklyn, N. Y.
William Menin...................................Philadelphia, Pa.
MAURICE MENSH...........................Washington, D. C.
Pasquale Frederic Metildi......................Rochester, N. Y.
Herman Frederic Meyer.......................Chicago, Ill.
Conn Lewis Milburn, Jr.......................M. C., U. S. Army
BEN NEELY MILLER, JR..................Columbia, S. C.
Edward Sidney Miller..........................Denver, Colo.
Joseph Leggett Miller, Jr......................Portland, Ore.
Reuben Mokotoff................................New York, N. Y.
MAX MALCOLM MONTGOMERY...........Chicago, Ill.
Donald Mahaney Moore.........................Ogden, Utah
Frank Hampton Moore.........................Bowling Green, Ky.
Charles Sol Morrow............................Butler, Pa. (V.A.)
VINCE MOSELEY.............................Charleston, S. C.
James Mercer Moss.............................Washington, D. C.
David Charles Mountain.......................Milwaukee, Wis.
Herbert Farrell Mulholland.....................New York, N. Y.
William Cameron Mumler.......................Los Angeles, Calif.
Daniel Wilbur Myers...........................Grosse Pointe, Mich.
WILLIAM NORWOOD MYHRE..............Spokane, Wash.

MEYER NAIDE...............................Philadelphia, Pa.
HERMAN RAPHAEL NAYER................New York, N. Y.
WILLIAM STRANGE NORTON, 2ND........New York, N. Y.
LEON JOSEPH NUMAINVILLE.............M. C., U. S. Army

NICHOLAS ROSARIO OCCHINO...........Johnson City, N. Y.
Richard Nolan O'Dell...........................Charleston, W. Va.
Earl Timothy Odom.............................Tuskegee, Ala. (V.A.)
Edward Joseph O'Donovan.....................Chicago, Ill.
DAN CLARK OGLE...........................M. C., U. S. Air Force
STANLEY WILLIAM OLSON................Chicago, Ill.
LUCY D. OZARIN.............................Washington, D. C.

Arthur Ewart Parks.............................Toronto, Ont., Can.
WILLIAM DARWIN PAUL..................Iowa City, Iowa
Alvin Joseph Paulosky.........................M. C., U. S. Navy
Morris Pearlmutter..............................New York, N. Y.
Maurice Lewis Pepper..........................Omaha, Nebr.
Harry Asher Pinsky.............................Camden, N. J.
VIRGIL ALLEN PLESSINGER...............Cincinnati, Ohio

Kemp Plummer.................................Richmond, Va. (V.A.)
LESTER JUNIOR POPE.......................M. C., U. S. Navy
ROBERT TRIGG PORTER...................Greeley, Colo.
Philip Preiser....................................Charleston, W. Va.
WILLIAM LYLE PROUDFIT...............Cleveland, Ohio
WILLIAM DITMARS PROVINCE...........Franklin, Ind.
Donald Frederick Purvis.......................Lincoln, Nebr.

RYLE AUGUST RADKE, SR.................M. C., U. S. Army
Eli Alberto Ramirez Rodriguez.................Santurce, P. R. (V.A.)
Charles Edward Rath............................Washington, D. C.
WILLIAM ALEXANDER READ.............Newport News, Va.
George Gordon Reader...........................New York, N. Y.
EDWARD PAUL REH........................St. Louis, Mo.
Aaron Julius Reiches.............................St. Louis, Mo.
Lawrence Berkley Reppert.......................San Antonio, Tex.
HENRY TUBBS RICKETTS.................Chicago, Ill.
Stanley Elpern Rosenbloom......................Pittsburgh, Pa.
PAUL SELBERT ROSS......................Columbus, Ohio
Aurelia Rozov...................................New York, N. Y.
Ira Lloyd Rubin................................New York, N. Y.
Joshua Rubinstein...............................Brooklyn, N. Y.
JOHN MARCUS RUMBALL...................Coral Gables, Fla. (V.A.)
ROBERT BRUCE RUTHERFORD, SR........Peoria, Ill.

Jacob Woodrow Savacool.......................Philadelphia, Pa.
Max Morton Scharf.............................Brooklyn, N. Y.
MILTON SCHLACHMAN....................Corona, N. Y.
Jakub G. Schlichter.............................Chicago, Ill.
Norman Grahn Schneeberg.......................Philadelphia, Pa.
Edmund Frederick Schroeder....................Cleveland, Ohio
Charles Schuman................................New York, N. Y.
Alfred Gego Selinger.............................Danville, Ill. (V.A.)
BERNARDO SEPULVEDA GUTIERREZ.....Mexico, D. F.
HERMAN HARVEY SHAPIRO...............Madison, Wis.
Archibald Daniel Sheeran........................New York, N. Y.
Jack Allan Sheinkopf............................Los Angeles, Calif.
SAMUEL SIMKINS..........................Philadelphia, Pa.
Leon Marcus Simms.............................Brooklyn, N. Y.
HOWARD NELLSON SIMPSON.............Springfield, Mass.
WILLIAM WESLEY SIMPSON...............Vancouver, B. C., Can.
JOHN LeROY SIMS..........................Madison, Wis.
John James Sloan...............................Corpus Christi, Tex.
Robert Benjamin Smith.........................Akron, Ohio
Charley Johnson Smyth..........................Denver, Colo.
KENNETH MALCOLM SODERSTROM......Seattle, Wash.
Sylvan Daniel Solarz............................Chicago, Ill.
Harry Aaron Solomon...........................New York, N. Y.
HYMAN U. SOLOVAY.......................Brooklyn, N. Y.
Charles Wallace Sorenson........................New York, N. Y.
GERALD ARTHUR SPENCER...............New York, N. Y.
CHARLES GASSAWAY SPICKNALL........U. S. Public Health Service
Clifford Leroy Spingarn.........................New York, N. Y.

Joseph Maurice Spitzer...........................New York, N. Y.
Maxwell Spring....................................New York, N. Y.
*Charles Stephen Stahlnecker.....................Media, Pa.
IRVING ELIHU STECK............................Chicago, Ill.
HUGH HENDERSON STEELE..............Detroit, Mich.
MAX HYMAN STEIN..............................Brooklyn, N. Y.
WILLIAM STEIN..................................M. C., U. S. Army
Franz Ulrich Steinberg............................St. Louis, Mo.
Harold Harvey Steinberg..........................Chicago, Ill.
ROBERT LEO STERN..........................Beverly Hills, Calif.
W. DEAN STEWARD............................Orlando, Fla.
Melvin Harold Stich...............................Brooklyn, N. Y.
William Hamilton Stimson.......................U. S. Public Health Service
Julius Edward Stolfi..............................Brooklyn, N. Y.
John Thompson Brown Strode....................M. C., U. S. Army
WILLIAM JOHN SULLIVAN................Bronxville, N. Y.
Paul Kent Switzer, Jr.............................Union, S. C.

Harry Taube.......................................New York, N. Y.
MATTHEW TAUBENHAUS..................Chicago, Ill.
JAMES GAVIN TELFER......................U. S. Public Health Service
Teodoro A. Texidor...............................Chicago, Ill.
GEORGE NEWTON THOMPSON...........Los Angeles, Calif.
W. TALIAFERRO THOMPSON, JR..........Richmond, Va.
NICHOLAS ARCHIBALD TIERNEY........Miami Beach, Fla.
James Herbert Topp...............................Rockford, Ill.

FRANKLIN JUDSON UNDERWOOD........Portland, Ore.
Paul Norman Unger...............................Miami Beach, Fla.

Thomas Edwin Van Sickle........................Akron, Ohio
Jules Victor, Jr...................................Savannah, Ga.

JOSEPH ADAM WAGNER....................Philadelphia, Pa.
Sholom Omi Waife...............................Philadelphia, Pa.
Milton Abraham Wald............................Brooklyn, N. Y.
Daniel John Waligora..............................M. C., U. S. Army
LOUIS ROBERT WASSERMAN.............New York, N. Y.
R(UTH) JANET WATSON....................Brooklyn, N. Y.
FREDERICK BEEMER WATTS..............Grosse Pointe Woods, Mich.
Malcolm Stuart McNeal Watts...................San Francisco, Calif.
LAWRENCE WECHSLER....................Pittsburgh, Pa.
Milton Ralph Weed...............................Detroit, Mich. (V.A.)
KENNETH DURHAM WEEKS, SR...........Rocky Mount, N. C.
Bernhard Joseph Weinberg......................Chicago, Ill.
James Irving Weinberg............................Atlanta, Ga.
Aaron Weisberg....................................Brooklyn, N. Y.
William Wolf Weissberg..........................Elizabeth, N. J.
Edward James Welch..............................Brookline, Mass.
ALLEN ABRAHAM WELKIND..............Newark, N. J.
Siegfried Werthammer............................Huntington, W. Va.
James Vincent White..............................Terre Haute, Ind.

* (MC), USNR

E(DWARD) GALE WHITING.................Berkeley, Calif.
R. HARVEY WHITING......................Edmonton, Alta., Can.
ROBERT WALLACE WILKINS..............Boston, Mass.
Ralph Clements Wilmore.......................Indianapolis, Ind.
Andrew Gerald Wilson...........................Detroit, Mich.
Raymond Thomas Wise........................New Britain, Conn.
Julius Wolf......................................New Hyde Park, N. Y.
SAMUEL ABRAHAM WOLFSON............Los Angeles, Calif.
Murray Alexander Woodside....................Ottawa, Ont., Can.
Claude-Starr Wright............................Columbus, Ohio
DONOVAN GEORGE WRIGHT..............Highland Park, Ill. (V.A.)

Louis Yesnick...................................Chicago, Ill.
Morton Yohalem.................................New York, N. Y.
Stephen Bennett Yohalem.......................New York, N. Y.
Arthur Foraker Young.........................Lakewood, Ohio
DENNISON YOUNG...........................Hartsdale, N. Y.
Ernest Harshaw Yount.........................Winston-Salem, N. C.

Saul Zukerman.................................Washington, D. C.

Dr. S. Marx White, Former President of the College, Honored

The Community Chest and Council of Hennepin County of Minneapolis on January 31, 1951, honored Dr. S. Marx White of Minneapolis for "distinguished community service." This is the annual distinguished service award. Dean Harold S. Diehl of the University of Minnesota Medical School in presenting the award referred to Dr. White as "typifying the ideal physician, the ideal citizen of any community."

Dr. White was President of the American College of Physicians in 1931-32, a past President of the Minnesota State Board of Health, a member of the Hennepin County Sanatorium Commission, a director of the Hennepin County Tuberculosis Association and President of the Community Chest and Council, and has been active in many other organizations.

Dr. Arden Freer, Acting Governor for the Veterans Administration

Because of the retirement of Dr. Paul B. Magnuson as Medical Director of the Veterans Administration, Dr. Arden Freer, Acting Chief Medical Director, becomes the Governor of the American College of Physicians for the Veterans Administration and all proposals for membership in the College must be cleared through Dr. Freer until further announcement.

American Board of Internal Medicine—Oral Examination

The American Board of Internal Medicine has announced the following schedule of oral examinations. It should be particularly noted that this schedule can include only those candidates who have not previously taken an oral examination of the Board:

St. Louis, Mo.—April 4-5-6, or 5-6-7, 1951
Philadelphia, Pa.—June, 1951 (Exact dates to be announced)
New York, N. Y.—(Dates to be announced)
San Francisco, Calif.—(Dates to be announced)

The closing date for acceptance of applications for the St. Louis examination was January 26, 1951; for the Philadelphia examination the closing date was March 1, 1951.

EXAMINATIONS—AMERICAN BOARD OF PEDIATRICS

Oral examinations of the American Board of Pediatrics will be held in Cincinnati, Ohio, March 30–31 and April 1, 1951; and in Atlantic City, N. J., May 5, 6, and 7, 1951. The only written examination of this board scheduled for 1951 was held on January 19.

UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE OFFERS POSTGRADUATE MEDICAL COURSES

The School of Medicine and University Extension of the University of California has announced the following courses at Los Angeles:

General Surgical Pathology Review; March 3–April 21, 1951; Saturday mornings; fee, $75.00.

Recent Advances in Hematology; February 14–April 4, 1951; Wednesday evenings; fee, $25.00.

Mycotic Infections; February 13–March 20, 1951; Tuesday evenings; No fee.

CORNELL MEDICAL COLLEGE ALUMNI WEEKEND

The Annual Meeting of the Alumni of Cornell University Medical College will be held in New York, N. Y., April 20–21, 1951. The third annual award to an alumnus for outstanding contributions to medicine will be conferred upon Dr. Connie M. Guion, Professor of Clinical Medicine at Cornell, who has long been active in the affairs of the College and has fostered the interests of women in medicine. The scientific program on April 20 will include clinical presentations by the staffs of New York Hospital, the Cornell divisions at Bellevue Hospital, and Memorial Hospital. A formal meeting on April 21 will be addressed on scientific subjects by several prominent alumni. On both days there will be held a scientific exhibit covering research work at the New York Hospital-Cornell Medical Center.

REAR ADMIRAL LAMONT PUGH, MC, USN, SWORN IN AS SURGEON GENERAL

Rear Admiral Lamont Pugh (MC), USN, was sworn in as the twenty-fifth Chief of the Navy's Bureau of Medicine and Surgery at a ceremony in the office of Secretary of the Navy, Francis P. Matthews, on January 29, 1951. Admiral Pugh succeeds Rear Admiral Clifford A. Swanson, and under conditions of the By-Laws of the American College of Physicians will become the College Governor for the Medical Corps of the U. S. Navy.

The World Health Organization and the Food and Agriculture Organization, which are agencies of the United Nations, have established twelve brucellosis research centers throughout the world. There are three centers in the Western Hemisphere; one in Argentine and one in Mexico. The third center is in the United States at the University of Minnesota. Dr. Wesley W. Spink, F.A.C.P., Professor of Medicine, is the Director. The purpose of these centers is to coördinate information on the control of brucellosis in animals and in man; to further research; and to exchange personnel for training and research.

Dr. Tom D. Spies, F.A.C.P., Director, Nutrition Clinic, Jefferson-Hillman Hospital, Birmingham, Ala., was presented with the Carlos J. Finlay Award on January 14 by the Cuban Government, for distinguished service in the field of medicine and public health. This award, the highest honor that can be given in the field of medicine in Cuba, was made by Senor Dr. Jose A. Rubio Padilla, Minister of Health of

Cuba. Honored with Dr. Spies were Dr. Elmer L. Henderson, President of the American Medical Association; Dr. George F. Lull, F.A.C.P., Secretary and General Manager of the American Medical Association; Dr. Paul de Kruif, Holland, Mich.; and Mr. Clyde P. Loranz, Secretary and General Manager of the Southern Medical Association.

The Senior Class of Jefferson Medical College of Philadelphia presented to the Medical College a portrait of Dr. Hobart A. Reimann, F.A.C.P., Magee Professor of Medicine and Head of the Department of Experimental Medicine, during a meeting in February attended by faculty, students and other physicians of Philadelphia.

Dr. George Morris Piersol, M.A.C.P., received the Award of Merit of the General Alumni Society of the University of Pennsylvania at the Founder's Day exercises, January 20, 1951, "for outstanding service to the University during the recent past."

Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, was recently elected President of the Society of United States Medical Consultants in World War II.

Colonel Elbert DeCoursey, (MC), USA, F.A.C.P., Director, Armed Forces Institute of Pathology, has been promoted to the rank of Brigadier General. General DeCoursey was formerly Commandant of the Army Medical Service Research and Graduate School, Army Medical Center, Washington, D. C.

Dr. Clyde W. Brunson, Commanding Officer of the U. S. Naval Hospital at Philadelphia and a Fellow of the American College of Physicians, on or about February 1, 1951, was promoted from the rank of Captain to that of Rear Admiral in the Medical Corps of the U. S. Navy.

Admiral Brunson is a graduate of the University of Pennsylvania School of Medicine, was awarded the Presidential Unit Citation for his participation in the defense of Pearl Harbor on December 7, 1941, and served aboard the hospital ship U.S.S. Solace in the South Pacific during the last war.

Dr. Don E. Nolan, F.A.C.P., Chief of Professional Services, Veterans Administration Center, Dayton, Ohio, has been named Manager of the 325 bed Veterans Administration Hospital now under construction at Seattle, Wash., which is expected to receive its first patients in April.

Dr. Edwin J. Rose, F.A.C.P., formerly Manager of the Veterans Administration Hospital, Minneapolis, Minn., has been appointed Assistant Director of the Hospital Operations Service, Veterans Administration Central Office, Washington, D. C.

Dr. Warren B. Cooksey, F.A.C.P., Detroit, Mich., was recently elected President of the United Health and Welfare Fund of Michigan.

Among the speakers at the Annual Neuropsychiatric Meeting, which was held at the Veterans Administration Hospital, North Little Rock, Ark., March 1–2, were Dr. Crawford N. Baganz, F.A.C.P., Lyons, N. J.; Dr. Saul Rosenzweig, F.A.C.P., Detroit, Mich.; Dr. Harold G. Wolff, F.A.C.P., New York, N. Y.; Dr. Edward D.

Greenwood (Associate), Topeka, Kans.; and Dr. Harvey J. Tompkins (Associate), Washington, D. C.

Dr. George H. Coleman, F.A.C.P., was recently elected Secretary of the Institute of Medicine of Chicago.

The University of Arkansas School of Medicine, Fayetteville, Ark., has announced the appointment of Colonel Charles T. Young, (MC), USA, F.A.C.P., as Assistant Professor of Medicine.

The Hektoen Institute for Medical Research has announced the appointment of Dr. Edmund F. Foley, F.A.C.P., Chicago, Ill., as a member of the Board of Trustees, and Dr. Benjamin M. Gasul, F.A.C.P., Chicago, Ill., as a Research Associate.

Among the guest speakers at the third annual Mid-Winter Radiological Conference, sponsored by the Los Angeles Radiological Society, which was held February 24–25, was Dr. W. Edward Chamberlain, F.A.C.P., Professor and Chairman of the Department of Radiology, Temple University School of Medicine, Philadelphia.

Seven Fellows of the American College of Physicians were among the speakers at the Atlanta Postgraduate Medical Assembly which was held February 5–7, in the Atlanta Municipal Auditorium. Included on the program were: Dr. Sara M. Jordan, Boston, Mass., "Cancer of the Stomach"; Dr. Carleton B. Peirce, Montreal, Que., "Diverticulosis and Diverticulitis"; Dr. F. William Sunderman, Atlanta, Ga., "Aspects of Serum Electrolytes with Particular Reference to Sodium and Potassium"; Dr. Warren W. Quillian, Coral Gables, Fla., "Care of the Premature Infant"; Dr. Richard B. Capps, Chicago, Ill., "Diagnosis and Treatment of Chronic Hepatitis"; Dr. Irvine H. Page, Cleveland, Ohio, "Diagnosis and Treatment of Hypertension"; and Dr. Walter Bauer, Boston, Mass., "Rheumatoid Arthritis, a Systemic Disease."

Among the speakers at the annual Watts Hospital Medical and Surgical Symposium which was held in Durham, N. C., February 14–15, were Dr. Bayard T. Horton, F.A.C.P., Rochester, Minn., whose subject was "Clinical Use of Histamine," and Dr. J. Warrick Thomas, F.A.C.P., Richmond, Va., who spoke on "Allergic Problems Demanding Prompt Treatment."

At the annual meeting of the Association for Research in Nervous and Mental Disease which was held in December in New York, N. Y., Dr. S. Bernard Wortis, F.A.C.P., New York, was elected President.

Dr. R. Bryan Grinnan, Jr., F.A.C.P., Norfolk, Va., was recently elected President of the Seaboard Medical Association at its meeting in Elizabeth City, N. C.

Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio, was recently appointed by the Advisory Board of the Society of U. S. Medical Consultants in World War II to head a committee which will concentrate on advising on assignment of consultants for Army hospitals in the United States. The aim of this committee will be to assure that every Army hospital in the United States will have available within a reasonable distance consultant skills which can be called upon as needed. A similar committee has been formed to carry on parallel work overseas.

Among the guest speakers at the annual meeting of the New Orleans Graduate Medical Assembly, which was held March 5–8, were Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn., "Effect of Cortisone and ACTH on Acute Rheumatic Fever"; Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Mich., "Clinical Implications of the Selye Alarm Reaction"; and Dr. Theron G. Randolph (Associate), Chicago, Ill., "Fatigue, Myalgia and Mental Symptoms of Allergic Origin."

Dr. Frank B. Queen, F.A.C.P., Portland, Ore., spoke on "The Problem of Thyroid Cancer," at the Interim Meeting of the Montana Medical Association, which was held in Helena, March 16–17.

The Temple University School of Medicine has announced the promotion of Dr. John Lansbury, F.A.C.P., Philadelphia, Pa., from Clinical Professor to Professor of Medicine. At the same time, Dr. Louis A. Soloff, F.A.C.P., was promoted from Assistant Professor to Associate Professor of Medicine.

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., and Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, Utah, were among the speakers at the Annual Postgraduate Convention of the College of Medical Evangelists, which was held in Los Angeles, March 11–16. Dr. Keefer spoke on "Selection of Anti-Infective Agents in the Prevention and Treatment of Disease." Dr. Wintrobe's subject was "Diagnosis and Treatment of Anemias."

At the Annual Clinical Conference of the Chicago Medical Society which was held March 6–9, the visiting speakers included: Dr. Esmond R. Long, F.A.C.P., Philadelphia, Pa., "Immunologic Considerations in Tuberculosis, with Special Reference to Vaccination"; Dr. Adolph L. Sahs, F.A.C.P., Iowa City, Iowa, "Diagnosis and Treatment of Meningitis"; Dr. Thomas H. Ham, F.A.C.P., Cleveland, Ohio, "Diagnosis and Treatment of Anemia"; Dr. Paul B. Beeson, F.A.C.P., Atlanta, Ga., "Effects of ACTH and Cortisone on Infectious Processes."

Six Fellows of the College were among the speakers at the fifth annual Michigan Postgraduate Clinical Institute, which was held in Detroit, March 14–16. The speakers and their subjects were: Dr. Russell S. Boles, Philadelphia, Pa., "Medical and Surgical Approach to Infectious Diseases of the Colon"; Dr. John E. Gordon, Boston, Mass., "Epidemiology of Accidents"; Dr. W. Paul Holbrook, Tucson, Ariz., participant on ACTH and Cortisone Panel; Captain George N. Raines, (MC), USN, "Somatic Manifestations of Depression"; Dr. Willard O. Thompson, Chicago, Ill., "Androgens and Estrogens in General Practice"; and Dr. Noyes L. Avery, Jr., Grand Rapids, Mich., "Pancreatitis, Clinical Manifestations and Treatment."

The University of Illinois College of Medicine has announced the promotion of Dr. Stuyvesant Butler, F.A.C.P., and Dr. Alva A. Knight, F.A.C.P., from Clinical Assistant Professors of Medicine to Clinical Associate Professors of Medicine.

Colonel Paul M. Crawford, (MC), USA, (Ret.), F.A.C.P., formerly Chief Surgeon at the Station Hospital, Fort Knox, Ky., has been appointed Director of Tuberculosis Control, Kentucky State Department of Health.

Training in Psychoanalytic Medicine is now being given at the State University Medical Center at New York City, College of Medicine, under the direction of Dr. Howard W. Potter, F.A.C.P., Professor of Psychiatry, who has set up within his department a Division of Psychoanalytic Medicine.

Dr. J. Russell Elkinton, F.A.C.P., Moylan, Pa., was among the recipients of fellowship awards for research in heart diseases provided by the American Heart Association for the academic year 1951–1952.

Brigadier General Elbert DeCoursey, (MC), USA, F.A.C.P., Director, Armed Forces Institute of Pathology, spoke on "Atomic Bomb Effects—Teaching Aids from Armed Forces Institute of Pathology," at the Eighteenth Annual Conference of Teachers of Clinical Radiology which was held in Chicago, Ill., February 10, 1951.

The National Foundation for Infantile Paralysis has awarded Dr. George Morris Piersol, M.A.C.P., Professor of Medicine and Chairman of the Department of Physical Medicine, University of Pennsylvania Graduate School of Medicine, a grant of $32,800 to study the heating effects on body cells of sound and electromagnetic waves. The project is an extension of the original Foundation-sponsored study of the therapeutic effects of heat in the treatment of polio and other conditions.

A new Blood Characterization and Preservation Laboratory was dedicated January 8 in Harvard University's Bussey Institution of Applied Biology. At the dedication ceremony, Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., Chairman of the Committee on Medical Sciences, Research and Development Board, U. S. Department of Defense, spoke on the need for preservation of the formed elements as well as of the plasma proteins of blood. Dr. William H. Sebrell, Jr., F.A.C.P., Director of the National Institutes of Health, spoke on the rôle of the U. S. Public Health Service in the national blood program.

Dr. Maxwell M. Wintrobe, F.A.C.P., Chairman of the Department of Medicine at the University of Utah School of Medicine, delivered the annual Loevenhart Lecture, which is presented by Phi Delta Epsilon, at the University of Wisconsin School of Medicine.

At a recent meeting of the Los Angeles Society of Allergy, Dr. M. Coleman Harris, F.A.C.P., Beverly Hills, Calif., was elected President, and Dr. Norman Shure (Associate), Beverly Hills, was elected Vice President.

For his "unending and numerous valued services in public health to the French Republic all over the world," Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health for the City and County of San Francisco, has been awarded the distinction and decoration of Commandeur dans l'Ordre du Ouissam Alaouite Chérifien by His Majesty, the Sultan of Morocco, through the Resident General of the French Republic in Morocco and the Consul General of France in San Francisco.

Dr. Russell M. Wilder, F.A.C.P., recently retired as Head of the Department of Medicine of the Mayo Foundation and Senior Consultant in Medicine of the Mayo

Clinic, Rochester, Minn., has been appointed Director of the recently established National Institute of Arthritis and Metabolic Diseases of the U. S. Public Health Service at Bethesda, Md.

————————

Dr. Milton J. Matzner, F.A.C.P., Brooklyn, N. Y., was recently appointed Attending Gastro-enterologist in charge of Gastro-enterology at the Jewish Hospital, Brooklyn.

————————

Dr. Anton J. Carlson, F.A.C.P., Professor Emeritus of Physiology, University of Chicago School of Medicine, was re-elected President of the National Society for Medical Research at its annual meeting on February 11, 1951. Dr. Andrew C. Ivy, F.A.C.P., Vice President of the University of Illinois and Head of the Chicago Professional Colleges of the University of Illinois, was re-elected Secretary-Treasurer.

Approval and authorization for the undertaking of two new projects was given at this meeting by the Board of Directors. One of these is the publication of a book summarizing the contributions of animals to medical progress and the welfare of human beings. The book will be illustrated with photographs. The other project is the production of a series of thirteen television films which will be based on real life visits to outstanding scientific institutions throughout the country.

OBITUARIES

DR. ERNEST SIDNEY MARIETTE

1888–1950

Ernest Sidney Mariette, B.S., M.D., F.A.C.P., died on October 29, 1950, after a long illness. He was born on January 3, 1888 in Blue Earth County, Minnesota. He attended the University of Minnesota and graduated from the Medical School in 1913. After completing an internship at the University of Minnesota Hospital and after serving as resident physician at Nopeming Sanatorium, he was appointed resident physician at Glen Lake in October, 1915, and it was he who admitted the first patient to enter this institution on January 4, 1916. In September, 1916, he was appointed Superintendent and Medical Director, a position which he held until his retirement on November 1, 1949.

Dr. Mariette's work as an administrator was outstanding. During the first ten years of his administration the Sanatorium expanded from a cottage-type institution with an original capacity of 50 beds to one with a multiple-storied hospital type construction with a capacity of 675 beds.

Dr. Mariette had a keen understanding of the fundamentals of treatment of tuberculosis. He recognized that bed rest formed the basis for all treatment but at the same time he was well aware of the value of special forms of therapy. Heliotherapy, pneumothorax, and various surgical procedures all were used as soon as the hospital facilities for carrying them out became available. He organized a full time medical staff, together with a visiting and consulting staff representing all of the specialties, thus making it possible to give complete medical and surgical care for all conditions, tuberculous and nontuberculous. And with a well qualified staff of nurses and dietitians the best of hospital care was made available. Thus, it is not surprising that Glen Lake was the first sanatorium to be approved by the American College of Surgeons in 1927.

Dr. Mariette was not satisfied to provide only the best of medical and hospital care. He felt that such ancillary services as medical social service, occupational therapy, library facilities, and adult education were essential to a complete program for the care of the tuberculous patient. The opening in 1931 of the building for vocational training provided adequate facilities for a teaching program which had been started in 1928 in collaboration with the Minneapolis Board of Education. He was well aware of the importance of all of these services, particularly as they were related to rehabilitation, in which he was a recognized leader.

Dr. Mariette was an assistant professor of medicine and a member of the faculty of the Graduate School of the University of Minnesota. He was well aware of the teaching facilities offered at the Sanatorium and under his sponsorship affiliation for students of nursing, medicine, dietetics, and occupational therapy were arranged. He also obtained approval of the American Medical Association for the Sanatorium as a place for fellowship training, and many young physicians from home and abroad availed themselves of the opportunity for study.

Dr. Mariette contributed more than sixty articles to the medical literature dealing with various phases of tuberculosis.

Dr. Mariette had a dynamic personality and possessed the qualities of leadership to an unusual degree. He had a keen mind and he was able to analyze the many problems that were presented to him quickly and forthrightly. His decisions were straightforward and without equivocation and he left no one in doubt as to where he stood on any important problem. He was gracious to all that he met and he was

dearly beloved by those who knew him best. Glen Lake Sanatorium stands as a monument to his untiring efforts and to his devotion in the fight against tuberculosis.

On June 9, 1923, Dr. Mariette married Anna Jones of Minneapolis who survives him. He also leaves a daughter, Grace, of Wayzata, Minnesota; a son, Edward, and three grandchildren of Glen Lake, Minnesota; and a brother, Percy A., of Arlington, N. J. They, with a host of friends, have suffered a great loss in his untimely death.

P. M. MATTILL, M.D., F.A.C.P.

DR. FRANKLIN WARREN WHITE

Franklin Warren White, B.S., M.D., F.A.C.P., was born in 1869 and died on December 19, 1950. He was a graduate of the Harvard Medical School in the class of 1895 and became an Instructor in Medicine at the Harvard Medical School and a Visiting Physician, and later a Consulting Physician, to the Boston City Hospital.

Dr. White was always intensely interested in internal medicine with special emphasis on gastro-enterology. After serving as Secretary of the American Gastro-enterological Association from 1911 to 1918, he was elected President in 1926. He was Chairman of the Section on Gastro-enterology of the American Medical Association in 1923. In 1935 he was a Delegate to the International Society of Gastro-enterology. Dr. White was a Diplomate of the American Board of Internal Medicine. He was elected a Fellow of the American College of Physicians in 1920, and served on the Board of Regents of the College from 1923 to 1926.

For many years after his retirement from the active staff of the Boston City Hospital, Dr. White served this institution as Consulting Physician. In this capacity he saw many patients on the wards with disorders of the gastrointestinal tract and over a period of years made an intensive clinical study of diseases of the liver and jaundice.

He was a man of great charm and wisdom—a striking figure, erect, athletic, with a bright twinkle in his eye. He always had a group of interested students following him on his rounds, and his advice was sought constantly by those who were puzzled by difficult problems.

His presence and influence will be missed by everyone who knew him. His standards were high, and by example he demonstrated the qualities of a fine physician.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. RALPH LEOPOLD SHANNO

Ralph Leopold Shanno, B.S., M.D., F.A.C.P., was born at Freeland, Pa., February 20, 1899, and died in Temple University Hospital on February 14, 1951, following a laminectomy performed on the morning of the same day.

Dr. Shanno received his B.S. degree from Purdue University in 1923 and his M.D. from Jefferson Medical College of Philadelphia in 1927. He interned for one year, 1927–28, at the Wilkes-Barre General Hospital and continued thereafter for three years as a Clinical Assistant. He manifested an early interest in surgery, but due to an infection of a finger, contracted from a patient during a surgical operation, a portion of his index finger had to be removed and this rendered it impractical for him to continue in the surgical field and accounts for his turning to the specialty of Internal Medicine and Cardiology. He pursued innumerable postgraduate courses in institutions in various parts of the United States, among which were many courses offered by the American College of Physicians. In later years his postgraduate efforts were

directed very largely toward the field of Cardiovascular Diseases. Few clinicians have ever shown a greater determination or a more sincere interest in qualifying in the best possible manner to care for patients. Only in the past autumn had he completed an A.C.P. course in Peripheral Vascular Diseases at the Mayo Clinic, and the day before his death he discussed with us registration in the A.C.P. Postgraduate Course in Clinical Electrocardiography at Detroit in March. For some years he came regularly one day a week to Philadelphia to work in the Cardiac Section of the Robinnette Foundation of the University of Pennsylvania under Dr. Charles C. Wolferth.

Dr. Shanno was an Assistant Instructor of Medicine at the University of Pennsylvania School of Medicine, Chief of the Medical Service and Cardiologist at the Mercy Hospital of Wilkes-Barre, Chief of the Medical Service and Associate Cardiologist at the Nesbitt Memorial Hospital at Kingston, Electrocardiographer at the Retreat State Hospital, Consultant in Cardiology to the Pittston and Wyoming Valley Homeopathic Hospitals and Attending Physician to the Veterans Administration.

He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1941, and a Life Member since 1945. He served during World War II as a Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve, and had been a very active worker in the Medical Society of the State of Pennsylvania, having served as·Secretary of the Section on Medicine, co-Chairman of the Committee on Rheumatic Diseases and member of the Committee on Nutrition. He was a regular attendant upon the meetings of the American College of Physicians, both in Eastern Pennsylvania and the national Annual Sessions. Also, he was a member of the Luzerne County Medical Society, Lehigh Valley Medical Society, the American Heart Association and a Fellow of the American Medical Association.

He was modest, kindly, considerate and generous, inspired to perform the greatest service within his power and opportunities. He is survived by his widow, Mrs. Grace V. Shanno, and a son, George.

EDWARD R. LOVELAND,
Executive Secretary, A.C.P.

DR. JOHN BERT JACKSON

John Bert Jackson, A.B., M.D., F.A.C.P., was born in Cooper, Mich., June 11, 1876, and died on November 3, 1950, in Kalamazoo, of arteriosclerotic heart disease. He is survived by his son, Howard C. Jackson, M.D., of Kalamazoo, Mich.

Dr. Jackson graduated from Kalamazoo College with a degree of A.B., in 1898, and from the Rush Medical College, M.D., in 1903. He was one of the pioneer radiologists of Western Michigan, and was a Diplomate of the American Board of Radiology. He was a Fellow of the American College of Radiologists, a member of the Radiological Society of North America, and a member of the American Roentgen Ray Society. In addition to these affiliations, he was President of the Michigan State Medical Society in 1926, and Past President of the Michigan State Trudeau Society and Kalamazoo Academy of Medicine. In 1920 he was elected a Fellow of the American College of Physicians.

As a roentgenologist, he served for many years on the staffs of the Borgess, the Bronson Methodist, and Kalamazoo State Hospitals.

Upon his death, the College has lost one of its oldest and most faithful members.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. HARRY LANDER JONES

Harry Lander Jones, M.D., F.A.C.P., was born December 22, 1877, in Marshall, Mo., the son of Theodore Clay Jones and Mary Steele Jones. He received his A.B. degree from Missouri Valley College, Marshall, Mo.; his M.D. degree from Washington University, St. Louis, in 1904.

After a year's internship at St. Louis City Hospital, he spent a year in practice in Marshall, then moved to Kansas City, Mo., where he continued in private practice until his death. Beginning in 1924 he was a part-time teacher in the Department of Medicine, University of Kansas School of Medicine, retiring in 1945 as Associate Professor.

Besides state, county and AMA memberships, he was a member of the Kansas City Southwest Clinical Society and a Diplomate of the American Board of Internal Medicine. In 1943 he was President of the Jackson County Medical Society; in 1945, Vice President of the Missouri State Medical Association.

In both World Wars he served without pay as examiner for local draft boards.

In 1912 he was married to Miss Winifred Reid of Kansas City, Mo. He is survived by her, and by three children: T. Reid Jones, M.D., Kansas City, Mo. (Associate of the College); Mrs. Theodore Weissinger, Wilmington, Del.; and Mrs. John C. Hosford, Arlington Heights, Ill.

Death occurred December 13, 1950, from coronary thrombosis, after seven hours' illness. He had had a previous coronary thrombosis in 1945.

During his forty years of practice in Kansas City he devoted his time exclusively to internal medicine. By his modesty and affable manner and from his ethical and honest methods he was universally admired and respected by all doctors.

PETER T. BOHAN, M.D., F.A.C.P.

DR. JOHN WILLIAM TRASK

John William Trask, M.D., a Fellow of the American College of Physicians since 1938, died on January 6, 1951. He was a graduate of the University of Michigan, Department of Medicine and Surgery, in 1901, and was a native of Bay City, Wash.

Dr. Trask entered the U. S. Public Health Service soon after graduation and remained active in this service until his retirement in 1941. Then he became the Commissioner of Public Health of Pittsfield, Mass., and held this post until 1946. He served in various Marine Hospitals in Detroit, Mich.; Fort Stanton, N. M.; Chicago, Ill.; Buffalo, N. Y.; Baltimore, Md.; Chelsea and Brighton, Mass. In most of these appointments he was Medical Officer in Charge and held the rank of Medical Director.

Dr. Trask was an extremely able administrator and student of Public Health. He wrote one of the best historical accounts of the Marine Hospitals in the United States, and at the time of his actual retirement he was the first Medical Director of the new Marine Hospital in Brighton, Mass. His standards of medical practice and hospital administration were extremely high, and he left a strong impression upon all who came in contact with him.

His contributions to medical literature were numerous and were concerned with subjects concerning the public health.

Those who had the privilege of knowing this quiet, forceful and able physician will miss him very much indeed. Dr. Trask had many friends, and he will long be remembered for his contributions to the public and to the U. S. Public Health Service, as well as to his associates.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. LANGDON TEACHOUT CRANE

Langdon Teachout Crane, A.B., M.D., F.A.C.P., Head of the Department of Medicine in the Highland Park General Hospital, Highland Park, Mich., died on January 3, 1951, after a long illness. Dr. Crane was born in Cleveland, Ohio, August 27, 1891. He was graduated from Western Reserve University in 1914, and from the Western Reserve University School of Medicine in 1917.

During World War I he served in the Medical Corps of the Army, with rank of Lieutenant. After the war was over, he started practice in Detroit, in 1919. He early became associated with Harper Hospital where he was in charge of the out-patient department until 1946. In 1927 he became associated with the Highland Park General Hospital. His chief interest was in Cardiology.

He was a member of Alpha Omega Alpha and was elected a Fellow of the American College of Physicians, March 31, 1940. From that time on, he was active in the local affairs of the College.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. DAVID ROWLAND WILLIAMS

David Rowland Williams, M.D., of Girard, Ohio, was born in 1863 near Oska-loosa, Iowa. In 1891 he received his medical degree from Columbus Medical College, one of the schools from which emerged the Ohio State University College of Medicine. He retired July 1, 1950, after 58 years of practice. He died at the North Unit of Youngstown Hospital, where he had been a staff member for many years, on October 15, 1950, after a short illness.

Dr. Williams was a medical pioneer in Trumbull County and served that community the entire 58 years he practiced medicine. He was the Liberty Township and Girard City Health Officer for 30 years, and had been an Associate of the American College of Physicians since 1925.

Dr. Williams was a village doctor of the old school. He was always cheerful, friendly, dignified, immaculately dressed and invariably wore a boutonniere in his lapel. He was deeply in love with his profession and considered it the greatest and noblest of all callings. He was an intimate friend and great admirer of the late Dr. George Crile.

CHARLES A. DOAN, F.A.C.P.,
Governor for Ohio

DR. KARL COULSON EBERLY, SR.

Karl Coulson Eberly, Sr., M.D., Fort Wayne, Ind., was born May 26, 1887, and died January 8, 1951. He received his medical degree from the University of Michigan Medical School in 1912 and was a member of the staff at St. Joseph's Hospital at Fort Wayne for many years and had been the Health Commissioner of Fort Wayne since 1935. At one time he was an Instructor in Physiology at the University of Michigan and later at the University of Minnesota. He was a member of Kappa Sigma and Phi Rho Sigma fraternities. He became an Associate of the American College of Physicians by virtue of membership in the American Congress on Internal Medicine, 1925. He was ever ambitious to avoid professional deterioration and looked upon membership in the College as an inspiration and the best antidote to prevent retrogression.

DR. ARTHUR JACKSON PATEK, SR.

Arthur Jackson Patek, Sr., A.B., M.D., F.A.C.P., dean of Wisconsin internists, died at a Milwaukee hospital of monocytic leukemia on October 12, 1950, one month before his eighty-second birthday, having been born in Milwaukee on November 11, 1868.

Dr. Patek received his A.B. from Johns Hopkins University in 1889, and his M.D. in 1892 from the University of Pennsylvania School of Medicine. He then studied in Berlin and at the University of Vienna Faculty of Medicine before returning to Milwaukee in 1896 to enter the practice of internal medicine, in which he was actively engaged until the time of his short terminal illness. Until then he had continued serving as Attending Physician to the Milwaukee, Columbia, and Mount Sinai Hospitals.

With the development of a four-year course in medicine by the University of Wisconsin Medical School in 1925, Dr. Patek became Preceptor-in-Charge of extramural clinical teaching at Milwaukee until World War II. Thereafter he was Preceptor Emeritus.

Dr. Patek was one of the founders of the Wisconsin Medical Journal, its editor for eight years, and contributor until October, 1950, when his last article entitled "The Journal Was Born" was published. He was a Past President of the Milwaukee Academy of Medicine and the Milwaukee County Medical Society. In 1913 he served as President of the Wisconsin State Medical Society, which further honored him in 1935 with its Council Award, the highest honor bestowed by the Society. During World War I he served in the Medical Corps, U. S. Army, with the rank of Captain. In 1917 he was elected a Fellow of the American College of Physicians and in 1937 he became a Diplomate of the American Board of Internal Medicine.

Dr. Patek was not only an outstanding physician, as attested by his record, but a gentleman of rare attributes, humble, confidence inspiring and capable; his was a full life devoted to constructive effort. Even to the last he was a frequent attendant at medical meetings. In other fields he was a bibliophile and an accomplished musician, a director of the Milwaukee Orchestral Association.

Surviving Dr. Patek are his wife, two daughters, and a son, Dr. Arthur J. Patek, Jr., Chief of the Division of Medicine of Mount Sinai Hospital, Cleveland, Ohio.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin